BIJLAGE
Richtlijn Wekedelentumoren

INITIATIEF
Nederlandse Vereniging voor Heelkunde

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Orthopaedische Vereniging
Nederlandse Vereniging voor Dermatologie en Venereologie
Nederlandse Vereniging voor Medische Oncologie
Nederlandse Vereniging voor Pathologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
Stichting Patiëntenplatform Sarcomen

MET ONDERSTEUNING VAN
Kennisinstituut Federatie Medisch Specialisten

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).

Inhoudsopgave

Verslag schriftelijke knelpuntanalyse richtlijn Wekedelentumoren

Datum uitnodiging verstuurd:
25 april 2022

Genodigde organisatie	1. Zijn er wat u betreft knelpunten rondom de zorg voor patiënten met wekedelentumoren die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	4. Andere vragen of opmerkingen t.a.v. het raamwerk	Reactie werkgroep
IGJ (Inspectie Gezondheidszorg en Jeugd)				Vanuit de Inspectie Gezondheidszorg en Jeugd zal er geen input worden gegeven.	Dank voor de reactie.
NFU (Nederlandse Federatie van Universitair Medische Centra)					-
NVZ (Nederlandse Vereniging van Ziekenhuizen)	-	-	De richtlijn/ kwaliteitsdocument dient organisatorisch, juridisch én financieel uitvoerbaar te zijn. Voor de verschillende soorten organisaties voor medisch specialistische zorg: algemene, categorale en topklinische ziekenhuizen en voor revalidatie-instellingen. Zonder ingrijpende consequenties op deze gebieden. In de samenvatting van de richtlijn/kwaliteitsdocument dient het onderdeel organisatie van zorg terug te komen. Het is daarbij van belang om inzicht te geven in het verschil tussen de huidige en de nieuwe situatie. Met als doel de impact van de aanbevelingen op organisatorische, juridische en financiële aspecten te kunnen beoordelen. Een implementatieplan met inzicht in de financiële, juridische en organisatorische consequenties is noodzakelijk om de impact van de aanbevelingen te beoordelen. Bij eventuele consequenties en/of knelpunten op het gebied van implementatie en naleving van de richtlijn/kwaliteitsdocument dienen aspecten zoals kosten, veranderde inzet van FTE, IT zaken of anderszins concreet te worden uitgewerkt. Tevens dient de richtlijn/kwaliteitsdocument rekening te houden met het verminderen van regeldruk/administratieve		Dank voor de reactie.

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			lasten, met de evaluatie van de huidige zorg en eventuele aangrenzende richtlijnen/kwaliteitsdocumente n. Ook dient de governance-afspraak 2019 (FMS/NFU/NVZ) te worden nagegaan om te beoordelen in welke categorie van haalbaarheid voor de uitvoering van de richtlijn/kwaliteitsdocument in de praktijk valt: categorie 1 (geen impact), 2 (twijfel) of 3 (grote impact). Afhankelijk van de categorie dient eventueel een BIA te worden uitgevoerd. Met als doel dat alle soorten organisaties voor medisch specialistische zorg de richtlijn uiteindelijk kunnen uitvoeren in de praktijk, zodra daar toezicht op wordt gehouden. Wij worden dus graag betrokken bij het vervolg en verzoeken u daarbij -indien van toepassing- een overzicht te verstrekken van de verschillen tussen de huidige en de nieuwe situatie om de impact beter te kunnen inschatten.		
Patiëntenfederatie Nederland				Bedankt voor je mail. Wij lezen dat de NFK en Stichting Patiëntenplatform Sarcomen zijn vertegenwoordigd m.b.t. de patiënten inbreng. Daarbij heeft de NFK de expertise voor deze richtlijn en zullen wij zelf niet deel nemen.	Dank voor de reactie.
STZ (Samenwerkende Topklinische opleidingsZiekenhuizen)					-
NAPA (Nederlandse Associatie Physician Assistants)	nee	nee	Beeldvormend onderzoek/stadiering		Deze onderwerpen worden uitgewerkt in de richtlijn.
ZiNL (Zorginstituut Nederland)					-
ZKN (Zelfstandige Klinieken Nederland)				Deze zorg wordt in klinieken niet geboden, daarom	Dank voor de reactie.

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				zullen wij geen inhoudelijke reactie geven	
ZN (Zorgverzekeraars Nederland)				Wij willen wel graag de uitkomst weten van de schriftelijke knelpunteninventarisatie en vernemen t.z.t. graag van u. Onze dank voor uw Uitnodiging om deel te nemen aan de (schriftelijke) knelpunteninventarisatie voor de richtlijn Wekedelentumoren. Helaas is dit onderwerp te specialistisch om als brancheorganisatie van zorgverzekeraars een nuttige bijdrage te leveren.	Dank voor de reactie.
VIG (Vereniging Innovatieve Geneesmiddelen)				Hartelijk dank voor onderstaand verzoek, wij komen hier zo snel mogelijk bij u op terug.	Dank voor de reactie.
Nederlandse Vereniging van Revalidatieartsen	Graag attenderen wij u erop bij de knelpuntenanalyse richtlijn wekedelentumoren, in overweging te nemen dat een NTRK-genfusie de onderliggende driver mutatie, zij het in zeer zeldzame gevallen, kan zijn bij wekedelentumoren.1,2 Er zijn momenteel twee EMA-geregistreerde TRK-remmers3,4 beschikbaar en vergoed voor patiënten met een aangetoonde TRK-fusie positieve tumor (ongeacht localisatie) middels larotrectinib en entrectinib. De therapeutische indicatie van larotrectinib is als volgt:				Dit onderwerp is buiten de prioritering gevallen, omdat het om een zeer zeldzane mutatie gaat.

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	Larotrectinib als monotherapie is geïndiceerd voor de behandeling van volwassen en pediatrische patiënten met solide tumoren die een neurotrofe tyrosinereceptorkinase (NTRK)-genfusie vertonen, - die een ziekte hebben die lokaal gevorderd of gemetastaseerd is of waarbij de kans groot is dat chirurgische resectie leidt tot ernstige morbiditeit, en - die geen bevredigende behandelopties hebben Voor larotrectinib zijn gepubliceerde data beschikbaar, waaronder die van de gepoolde dataset in Lancet Oncology5 en een publicatie met betrekking tot de potentiële vergelijkende effectiviteit op lange termijn van larotrectinib versus de standaardbehandeling voor de behandeling van gemetastaseerde TRK-fusie-schildklierkanker, colorectale kanker en wekedelensarcoom.6 Voor larotrectinib is een specifieke dataset bij volwassen patiënten met TRK-fusie-positieve sarcomen gepresenteerd op het CTOS 2021.7 1. Forsythe A, et al. Ther Adv Med Oncol 2020, Vol. 12: 1–10.				

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	2. Siozopoulou V, et al. Diagnostics (Basel) 2021; 11(3): 478. 3. SmPC larotrectinib, 02/2022. 4. SmPC entrectinib, 8/2021. 5. Hong DS, et al. Lancet Oncol 2020 Apr;21(4):531-540. 6. Suh K, et al. J Manag Care Spec Pharm, 2022 Jun;28(6):622-630. 7. Kummar S, et al. Larotrectinib in Adult Patients with TRK Fusion Sarcomas: Updated Efficacy				
NVKNO	Nee, geen aanvullingen los van de vraag of de behandeling van patiënten in een gespecialiseerd centrum moet plaatsvinden of alleen de bespreking hiervan. Maw een pt met een weke dele tumor in het HMC wordt besproken in het LUMC en een behandeling zou dan weer in het HMC kunnen. Heeft dit de voorkeur of zijn jullie van mening dat dit in een centrum moet?	nee	Adequate therapie valt of staat bij goede diagnostiek. Focus zou moeten liggen bij beeldvorming en pathologie		Beiden punten worden meegenomen in de uitwerking van de richtlijn.
NVMDL				Vanuit de NVMDL zijn geen aanvullingen of opmerkingen op het conceptraamwerk. Ter info, voor MDL-artsen is de richtlijn met name relevant ten aanzien van de GIST en desmoid tumoren. Voor deze zeldzame tumoren zijn ook de internationale richtlijn van de ESMO richtinggevend.	In deze richtlijn wordt zoveel mogelijk aangesloten bij de internationale ESMO richtlijn.
VRA				Vanuit de VRA zijn er geen knelpunten aangedragen voor de richtlijn Wekedelentumoren.	Dank voor de reactie.

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NVDV				Eerder heeft de NVDV adhesie verleend aan de herziening van de richtlijn Wekedelentumoren en daarbij aangegeven het zeer wenselijk te vinden om hierbij primair betrokken te worden. De mailcorrespondentie hierover voeg ik hierbij toe (laatste 2 bijlagen). Uit onderstaande mail blijkt nu dat we niet primair betrokken zijn bij de herziening van deze richtlijn, we hebben ook geen reactie gezien op de mailcorrespondentie tussen Evelien Kok en Kim Geelen waarin de NVDV haar wens tot primaire betrokkenheid heeft geuit. Nu is Kim sinds kort niet meer in dienst van de NVDV dus mogelijk is er een mail aan haar over dit onderwerp tussen de wal en het schip geraakt. Het bestuur en de domeingroep Oncologie van de NVDV willen als gemandateerde dermatoloog (mevrouw dr. R.R. Van den Bos) graag afvaardigen voor de projectgroep en vernemen graag jullie reactie. (Evelien Kok NVvH en directie NVDV Frans Meulenberg en Jannes van Everdingen staan ter informatie in de cc.)	Dr. R.R. Van den Bos is toegevoegd als werkgroeplid.

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NVKG				Er zijn voor deze uitvraag rondom knelpuntenanalyse geen specifieke aandachtspunten aangegeven. We verwijzen wel graag naar het addendum Ouderenproof maken van richtlijnen, waarbij specifieke aandachtspunten worden benoemd om binnen een richtlijn ondersteuning te kunnen bieden bij het behandelen van de oudere patiënt die vaak te maken hebben met co morbiditeit en multimorbiditeit.	Dank voor de reactie.
NVOG	De NVOG heeft geen op- of aanmerkingen				
NVZA				De NVZA heeft helaas geen knelpunten om aan te leveren voor deze richtlijn.	Dank voor de reactie.
Nederlandse Vereniging voor Psychosociale Oncologie (NVPO)	Wij zouden graag zien dat er één of meer uitgangsvragen worden toegevoegd over de paramedische en psychosociale zorg. U kunt hierbij denken aan: 'Hoe (vaak) en wanneer in het gehele traject moeten zaken omtrent kwaliteit van leven en behoefte aan aanvullende paramedische en psychosociale zorg aan de orde komen'.		Wij kunnen geen prioriteit aanbrengen in de medisch-technische uitgangspunten, maar verzoeken wel om meer aandacht te geven cq het verder uit te werken van zaken op het gebied van kwaliteit van leven en aanvullende paramedische en psychosociale zorg.		De kwaliteit van leven zal in verschillende modules meegenomen worden bij de tot standkoming van de aanbevelingen en ook in de module over Voorlichting worden meegenomen. In de module voorlichting zal ook aandacht besteed worden aan aanvullende paramedische en psychosociale zorg.

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NHG				Hartelijk dank voor onderstaand verzoek. We hebben dit intern besproken en daaruit kwam de volgende reactie: We zouden u graag willen verzoeken in de doelgroep onderscheid te maken tussen de primaire doelgroep en andere beroepsgroepen voor wie de richtlijn zinvolle informatie biedt, maar die niet worden geacht deze te volgen. Bijvoorbeeld als volgt: Voor wie is deze richtlijn bedoeld? De richtlijn is primair bedoeld voor (…). Daarnaast kan de richtlijn ook geraadpleegd worden door huisartsen, (…). Tevens hebben we het verzoek om bij de doelgroep aan te geven dat het tweedelijns patiënten betreft. Dit is nu onduidelijk. Vanwege het tweedelijnskarakter van de richtlijn zullen we geen knelpunten aanleveren.	Bij de afbakening op de startpagina zullen we aangeven dat deze richtlijn is bestemd voor alle zorgverleners in tweede lijn die betrokken zijn bij de zorg voor patiënten met wekedelentumoren.
IKNL				Vanuit IKNL (tumorteam bot- en wekedelen) maken wij geen gebruik van uw uitnodiging om bij te dragen aan deze knelpunteninventarisatie. Wij laten dit graag over aan de diverse zorgprofessionals in het veld.	Dank voor de reactie.
KNGF	Nee	Nee	Kwaliteit van leven	Onze complimenten over het raamwerk. We hebben niet veel input.	Dank voor de reactie.
NZa					-

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V&VN				Verzoek bij relevante V&VN afdelingen uitgezet, maar geen reactie/knelpunten ontvangen.	Dank voor de reactie.
NIP	Wij zouden graag zien dat er één of meer uitgangsvragen worden toegevoegd over de paramedische en psychosociale zorg. U kunt hierbij denken aan: 'Hoe (vaak) en wanneer in het gehele traject moeten zaken omtrent kwaliteit van leven en behoefte aan aanvullende paramedische en psychosociale zorg aan de orde komen'.			Wij kunnen geen prioriteit aanbrengen in de medisch-technische uitgangspunten, maar verzoeken wel om meer aandacht te geven cq het verder uit te werken van zaken op het gebied van kwaliteit van leven en aanvullende paramedische en psychosociale zorg.	De kwaliteit van leven zal in verschillende modules meegenomen worden bij de tot standkoming van de aanbevelingen en ook in de module over Voorlichting worden meegenomen. In de module voorlichting zal ook aandacht besteed worden aan aanvullende paramedische en psychosociale zorg.
NVPC				De NVPC heeft in deze ronde geen aanvullingen op knelpunteninventarisatie	Dank voor de reactie.
NVVP				Graag laat ik je hierbij weten dat wij geen input hebben voor de knelpunteninventarisatie. Ook hebben we nog geen deelnemer voor de werkgroep gevonden. Zodra dat verandert, laat ik het weten.	Dank voor de reactie.
Werkgroepleden / meelezers					
Nederlandse Vereniging voor Heelkunde NVvH					
NVVvH					
Nederlandse Internisten Vereniging (NIV)					
Nederlandse Orthopaedische Vereniging					
Nederlandse Vereniging voor Nucleaire Geneeskunde					
Nederlandse Vereniging voor Pathologie					

Genodigde organisatie	1. Zijn er wat u betreft knelpunten rondom de zorg voor patiënten met wekedelentumoren die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	4. Andere vragen of opmerkingen t.a.v. het raamwerk	Reactie werkgroep
Nederlandse Vereniging voor Radiologie					
Nederlandse Vereniging voor Radiotherapie en Oncologie (14.06.2022 verstuurd)					
NFK Nederlandse Federatie van Kankerpatiëntenorganisaties					
Stichting Patiëntenplatform Sarcomen					

Module 1 – Diagnostiek tumor

Search and select
A systematic review of the literature was performed to answer the following question:
What is the optimal imaging protocol in patients with a suspected soft tissue sarcoma?

P = Patients with (suspected) soft tissue sarcoma
I = Computed tomography (CT) and ultrasound
C = Magnetic resonance imaging (MRI)
R = Clinical course, histology (biopsy)
O = Diagnostic performance

Relevant outcome measures
A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until September 20, 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 789 hits. Studies were selected based on the following criteria: fit PICO, systematic reviews, randomized controlled trials, observational studies, article in English or Dutch. 27 studies were initially selected based on title and abstract screening. After reading the full text, 25 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results
Two (2) studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature
Description of studies
Dubreuil (2017) performed a systematic review of cohort studies that investigated the diagnostic performance of diffusion-weighted (DWI) MRI and ^{18}F-FDG-PET imaging as methods to diagnose uterine sarcomas. The review included seven studies (one prospective, six retrospective) that investigated DWI-MRI. In total, 504 patients were included.

Martin (2020) performed a systematic review of cohort studies that investigated the performance of MRI and PET imaging as methods to diagnose malignant peripheral nerve sheath tumors (MPNSTs). The review meta-analyzed 35 studies, of which sixteen regarded MRI characteristics. These sixteen studies included 925 patients, of whom 48% had neurofibromatosis type 1.

Results
MRI
Uterine sarcomas
Sensitivity
Four studies in Dubreuil (2017) reported the sensitivity of MRI: Lin, 2016; Thomas, 2013; Zhang, 2014, and Namimoto, 2009. They reported sensitivities of 81% to 100%. No pooled sensitivity could be calculated due to the absence of underlying numbers.

Specificity
Three studies in Dubreuil (2017) reported the specificity of MRI: Lin, 2016; Zhang, 2014, and Namimoto, 2009. The reported specificities ranged from 36% to 100%. No pooled sensitivity could be calculated due to the absence of underlying numbers.

Area under the curve
One study in Dubreuil (2017) reported an AUC (Lin, 2016). An AUC of 0.92 was reported for contrast-enhanced imaging, 0.68 for diffusion weighted imaging (DWI), 0.65 for T1 weighted imaging, 0.60 for T2 weighted imaging, and 0.74 for DWI combined with apparent diffusion coefficient values.

Accuracy
One study in Dubreuil (2017) reported on accuracy (Lin, 2016). An accuracy of 94% was reported for contrast-enhanced imaging, and 52% for DWI.

Malignant peripheral nerve sheath tumors
Sensitivity
Ill-defined margins
Nine studies in Martin (2020) reported the sensitivity of the presence of ill-defined margins on MRI. The (Bayesian) pooled sensitivity was 0.94 (95% credibility interval: 0.88 to 0.98).
Perilesional edema
Five studies in Martin (2020) reported the sensitivity of the presence of perilesional edema on MRI. The (Bayesian) pooled sensitivity was 0.95 (95% credibility interval: 0.83 to 1.00).

Specificity
Ill-defined margins
Nine studies in Martin (2020) reported the specificity of the presence of ill-defined margins on MRI. The (Bayesian) pooled specificity was 0.52 (95% credibility interval: 0.40 to 0.65).
Perilesional edema
Five studies in Martin (2020) reported the specificity of the presence of perilesional edema on MRI. The (Bayesian) pooled specificity was 0.95 (95% credibility interval: 0.83 to 1.00).

Positive likelihood ratio
Ill-defined margins
Nine studies in Martin (2020) reported the positive likelihood ratio of the presence of ill-defined margins on MRI. The (Bayesian) pooled positive likelihood ratio was 11.03 (95% credibility interval: 3.83 to 31.62).
Perilesional edema
Five studies in Martin (2020) reported the positive likelihood ratio of the presence of perilesional edema on MRI. The (Bayesian) pooled positive likelihood ratio was 3,415.18 (95% credibility interval: 3.15 to 5,948.77).

Negative likelihood ratio
Ill-defined margins
Nine studies in Martin (2020) reported the negative likelihood ratio of the presence of ill-defined margins on MRI. The (Bayesian) pooled negative likelihood ratio was 0.51 (95% credibility interval: 0.36 to 0.66).
Perilesional edema
Five studies in Martin (2020) reported the negative likelihood ratio of the presence of perilesional edema on MRI. The (Bayesian) pooled negative likelihood ratio was 0.38 (95% credibility interval: 0.12 to 0.69).

PET-CT

Malignant peripheral nerve sheath tumors

Sensitivity

SUV_{max}

Thirteen studies in Martin (2020) reported the sensitivity of SUV_{max} on PET-CT. The (Bayesian) pooled sensitivity was 0.94 (95% credibility interval: 0.91 to 0.97). A median (IQR) cut-off value of 3.96 (2.35 to 6.1) was used over the underlying studies.

Tumor-to-liver ratio

Seven studies in Martin (2020) reported the sensitivity of the tumor-to-liver ratio on PET-CT. The (Bayesian) pooled sensitivity was 0.93 (95% credibility interval: 0.87 to 0.97). A median (IQR) cut-off value of 1.77 (1.38 to 3.0) was used over the underlying studies.

Specificity

SUV_{max}

Thirteen studies in Martin (2020) reported the specificity of SUV_{max} on PET-CT. The (Bayesian) pooled specificity was 0.81 (95% credibility interval: 0.76 to 0.87).

Tumor-to-liver ratio

Seven studies in Martin (2020) reported the specificity of the tumor-to-liver ratio on PET-CT. The (Bayesian) pooled specificity was 0.79 (95% credibility interval: 0.70 to 0.86).

Positive likelihood ratio

SUV_{max}

Thirteen studies in Martin (2020) reported the positive likelihood ratio of SUV_{max} on PET-CT. The (Bayesian) pooled positive likelihood ratio was 5.22 (95% credibility interval: 3.74 to 7.51).

Tumor-to-liver ratio

Seven studies in Martin (2020) reported the positive likelihood ratio of the tumor-to-liver ratio on PET-CT. The (Bayesian) pooled positive likelihood ratio was 4.69 (95% credibility interval: 2.89 to 7.41).

Negative likelihood ratio

SUV_{max}

Thirteen studies in Martin (2020) reported the negative likelihood ratio of SUV_{max} on PET-CT. The (Bayesian) pooled negative likelihood ratio was 0.07 (95% credibility interval: 0.03 to 0.12).

Tumor-to-liver ratio

Seven studies in Martin (2020) reported the negative likelihood ratio of the tumor-to-liver ratio on PET-CT. The (Bayesian) pooled negative likelihood ratio was 0.09 (95% credibility interval: 0.03 to 0.18).

Level of evidence of the literature

Uterine sarcomas

The level of evidence regarding the sensitivity of MRI to diagnose uterine sarcomas started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the specificity of MRI to diagnose uterine sarcomas started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the accuracy of MRI to diagnose uterine sarcomas started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

Malignant peripheral nerve sheath tumors

MRI

The level of evidence regarding the sensitivity of MRI to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by three levels to Very low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the specificity of MRI to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the positive predictive value of MRI to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded to Low by two levels because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the negative predictive value of MRI to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded to Low by two levels because of study limitations (risk of bias), and number of included patients (imprecision).

PET-CT

The level of evidence regarding the sensitivity of PET-CT to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the specificity of PET-CT to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the positive predictive value of PET-CT to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

The level of evidence regarding the negative predictive value of PET-CT to diagnose malignant peripheral nerve sheath tumors started as High (systematic reviews) and was downgraded by two levels to Low because of study limitations (risk of bias), and number of included patients (imprecision).

Conclusions

Uterine sarcomas

Low GRADE	The evidence suggests that MRI is a sensitive method to distinguish uterine sarcomas from benign lesions in patients with a suspected uterine sarcoma. *Source: Dubreuil, 2017*
Low GRADE	The evidence suggests that MRI detects uterine sarcomas with a reasonable specificity in patients with a suspected uterine sarcoma. *Source: Dubreuil, 2017*
Low GRADE	The evidence suggests that MRI is a sensitive method to distinguish uterine sarcomas from benign lesions in patients with a suspected uterine sarcoma. *Source: Dubreuil, 2017*

Malignant peripheral nerve sheath tumors
MRI

Very low GRADE	The evidence is unclear about the sensitivity of MRI to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected uterine sarcoma. *Source: Martin, 2020*
Low GRADE	The evidence suggests that MRI detects malignant peripheral nerve sheath tumors with a good specificity in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*
Low GRADE	The evidence suggests that MRI is a sensitive method to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*
Low GRADE	The evidence suggests that MRI is a sensitive method to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*

PET-CT

Low GRADE	The evidence suggests that PET-CT is a sensitive method to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*
Low GRADE	The evidence suggests that PET-CT detects malignant peripheral nerve sheath tumors with a reasonable specificity in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*
Low GRADE	The evidence suggests that PET-CT is a sensitive method to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*
Low GRADE	The evidence suggests that PET-CT is a sensitive method to distinguish malignant peripheral nerve sheath tumors from benign lesions in patients with a suspected malignant peripheral nerve sheath tumor. *Source: Martin, 2020*

Kennislacunes
What is the optimal imaging protocol in patients with a suspected soft tissue sarcoma?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
alle	1-3	Minimaal, geen nieuwe modaliteiten voorgesteld	-	-	geen	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Opzet template wekedelentumor

Locatie		Extremiteit, hoofd, hals, thorax, abdomen	[Vrij tekst]
	Zijdigheid	Links of rechts	Links/rechts (aanvinken)
	Diepte	Oppervlakkig: buiten fascie, cutis, subcutis, Diep: Binnen de fascie: intra en/of intermusculair, retroperitoneum incl peritesticulair, abdominaal	Binnen/ buiten de fascie (aanvinken) Intra/intermusculair (aanvinken) [Vrij tekst]

	Anatomie	Welk compartiment en spier(en)	[Vrij tekst]
Eigenschappen:	**Invasie**	Musculair, ossaal, articulaire betrokkenheid, pleura, anderszins.	Indien aanwezig: [Vrij tekst]
	Betrokkenheid/relatie:	Neurovasculaire bundel, pezen, mate van encasement	Encasement vasculaire bundel wel of niet (aanvinken). Graden circumferentie: [Vrij tekst]
	Begrenzing:	Scherp, onscherp, vorm	[Vrij tekst]
	Karakteristieken MRI	Signaalintensitiet t.o.v spier	T1 Hypointens, intermediair, hyperintens (aanvinken). T2: Hypointens, intermediair, hyperintens (aanvinken). Perilesionaal oedeem (ja/nee) [Vrij tekst]
	Aanwezigheid van	Hemosiderine Calcificaties Myxoid Fibreus weefsel/banden	Ja/nee Ja/nee Ja/nee Ja/nee
	Mate van aankleuring na i.v. contrast **DCE: aankleuringspatroon:**	Homogeen Heterogeen Necrose aanwezig Snel, steile up-slope, maligne, evt washout Intermediair, onzeker benigne/maligne Langzaam,benigne aspect	Homogeen/heterogeen (aanvinken) Aanwezig ja/nee Geschatte percentage: [getal] [Vrij tekst]
	Indien aanwezig DWI	Diffusierestrictie: T2 shine through	Ja/ nee (aanvinken) Ja/ nee (aanvinken)
Grootte:		Afmetingen in 3 richtingen (AP x LR x CC) (gemeten op best mogelijke sequentie in mm)	AP [getal] x LR x CC getal] x [getal]
Andere tumor lokaties:		Skip of multiple lesions Lymfadenopathie	Ja/nee: [Vrij tekst] Ja/nee: [Vrij tekst]
Conclusie:		Radiologische waardering: benigne, maligne of onzeker	Radiologische waardering:

		benigne/maligne De radiologische differentiaaldiagnose:	Benigne/maligne/ of onzeker benigne/maligne (aanvinken) DD: [Vrij tekst]

Evidence table

Research question: Wat is het optimale beeldvormend onderzoek dat gedaan moet worden bij patiënten met verdenking op wekedelensarcomen?

Study reference	Study characteristics	Patient characteristics	Index test	Comparison comparator test	Follow-up	Outcome measures and effect size	Comments
Dubreuil, 2017 study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of cohort studies *Literature search between January 2016 and February 2016* A: Lin, 2016 B: Thomassin-Naggara, 2013 C: Zhang, 2014 D: Tamai, 2008 E: Sato, 2014 F: Namimoto, 2009 G: Takasi, 2015 <u>Study design</u>: A: prospective cohort (PC) B: retrospective cohort (RC) C: RC D: RC E: RC F: RC G: RC	Inclusion criteria SR: studies of ^{18}F-FDG-PET and MRI, staging, restaging, tumor characterization of uterine sarcomas Exclusion criteria SR: case reports, letters to the editors/correspondence, studies that were not the most recent of the authors teams, fewer than 5 cases, no DWI-MRI, *7 studies included* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> A: 39; not reported (not reported)	A: MRI with contrast enhancement B: diffusion weighted imaging (DWI) MRI in combination with a prognostic model C: diffusion weighted imaging (DWI) MRI D: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI E: diffusion weighted imaging (DWI) MRI F: T2-weighted MRI imaging G: diffusion weighted imaging (DWI) MRI	A: diffusion weighted imaging (DWI) MRI B: histology C: histology D: histology E: histology F: histology G: histology	Not applicable	<u>Outcome measure-1</u> A: sensitivity: 88% (CE), 100% (DWI) (95% CI: not reported) B: sensitivity: 92.4% (95% CI: not reported) C: sensitivity: 81% (95% CI: not reported) D: sensitivity: not reported (95% CI: not reported) E: sensitivity: not reported (95% CI: not reported) F: sensitivity: 100% (95% CI: not reported) G: sensitivity (95% CI: not reported) Pooled effect: not reported <u>Outcome measure-2</u> A: specificity: 96% (CE), 36% (DWI) (95% CI: not reported) B: specificity (95% CI: not reported) C: specificity: 62% (95% CI: not reported) D: specificity (95% CI: not reported) E: specificity (95% CI: not reported)	Only a few studies on MRI or PET in patients suspected to have uterine sarcoma. However, DWI-MRI appeared to be able to distinguish benign and malignant lesions. PET generally needs other data to be able to make the distinction. Personal remarks: PRISMA used to assess level of evidence over the included studies, no pooled data, and limited information about study characteristics in general. No sensitivity analyses were performed. Level of evidence: Sensitivity MRI: Low GRADE (-1 RoB, -1 imprecision, low nr of pt) Specificity MRI: Low GRADE (-1 RoB, -1 imprecision, low nr of pt) AUC MRI: Low GRADE (-1 RoB, -2 imprecision, low nr of pt)

	Setting and Country: A: outpatient clinic, Taiwan B: outpatient clinic, France C: outpatient clinic, People's Republic of China D: outpatient clinic, Japan E: outpatient clinic, Japan F: outpatient clinic, Japan G: outpatient clinic, Japan Funding and conflicts of interest A: not reported B: not reported C: not reported D: not reported E: not reported F: not reported G: not reported	B: 51; not reported (not reported) C: 43; not reported (not reported) D: 43; not reported (not reported) E: 91; not reported (not reported) F: 103; not reported (not reported) G: 134; not reported (not reported) *Sex:* 100% female patients with suspected uterine sarcoma in all studies Groups comparable at baseline? Not applicable				F: specificity: 100% (95% CI: not reported) G: specificity (95% CI: not reported) Pooled effect: not reported Outcome measure-3 A: Area under the curve (AUC): 0.92 (CE), 0.68 (DWI), 0.65 (T1W), 0.60 (T2W), 0.74 (DWI+ADC) (95% CI: not reported) B: AUC (95% CI: not reported) C: AUC (95% CI: not reported) D: AUC (95% CI: not reported) E: AUC (95% CI: not reported) F: AUC (95% CI: not reported) G: AUC (95% CI: not reported) Pooled effect: not reported Outcome measure-4 A: accuracy: 94% (CE), 52% (DWI) (95% CI: not reported) B: accuracy (95% CI: not reported) C: accuracy (95% CI: not reported) D: accuracy (95% CI: not reported) E: accuracy (95% CI: not reported) F: accuracy (95% CI: not reported)	Accuracy MRI: Low GRADE (-1 RoB, -2 imprecision, low nr of pt)

						G: accuracy (95% CI: not reported) Pooled effect: not reported	
Martin, 2020 study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of cohort studies *Literature search between January 2000 and November 2019* A: Ahlawat, 2018 B: Ahlawat, 2019 C: Azizi, 2018 D: Bensaid, 2007 E: Benz, 2010 F: Bredella, 2007 G: Broski, 2016 H: Cardona, 2003 I: Chhabra, 2011 J: Chirindel, 2015 K: Combemale, 2014 L: Cook, 2017 M: Demehri, 2014 N: Derlin, 2013 O: Fayad, 2014 P: Ferner, 2000 Q: Ferner, 2008 R: Furniss, 2007 S: Hummel, 2010 T: Johansson, 2014	Inclusion criteria SR: studies including both extracranial malignant peripheral nerve sheath tumors (MPNSTs) and benign peripheral nerve sheath tumors (BPNSTs), description using MRI or FDG-PET and/or liquid biopsy. Exclusion criteria SR: case reports, letters to the editors/correspondence, lack of full-text article, conference abstracts, reviews. *43 studies included* <u>Important patient characteristics at baseline</u>:	A: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI B: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI C: D: E: F: G: T1-weighted, and T2-weighted MRI H: I: T1-weighted, and T2-weighted MRI J: K: L: M: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI N: T1-weighted, and T2-weighted MRI O: T1-weighted, and T2-weighted MRI; MRS P: Q: R: S:	A: B: PET-CT C: PET-CT D: PET-CT E: PET-CT F: PET-CT G: PET-CT H: PET-CT I: J: K: PET-CT L: PET-CT M: N: PET-CT O: P: PET-CT Q: PET-CT R: S: T: U: PET-CT V: W: PET-CT X: Y: Z: AA: PET-CT AB: PET-CT AC: PET-CT AD: PET-CT AE: AF:	Not applicable	<u>Outcome measure-1 - Pooled</u> DWI-MRI A: Ill-defined margins - pooled sensitivity: 0.52 (95% CI: 0.40 to 0.65) A: Ill-defined margins - pooled specificity: 0.94 (95% CI: 0.88 to 0.98) A: Ill-defined margins - pooled positive likelihood ratio: 11.03 (95% CI: 3.83 to 31.62) A: Ill-defined margins - pooled negative likelihood ratio: 0.51 (95% CI: 0.36 to 0.66) <u>Outcome measure-2 Pooled</u> DWI-MRI B: Perilesional edema - pooled sensitivity: 0.65 (95% CI: 0.38 to 0.87) B: Perilesional edema - pooled specificity: 0.95 (95% CI: 0.83 to 1.00) B: Perilesional edema - pooled positive likelihood ratio: 3415.18 (95% CI: 3.15 to 5948.77) B: Perilesional edema - pooled negative likelihood	Systematic review and meta-analysis of studies regarding the diagnostic accuracy of MRI and PET-CT for the diagnosis of peripheral nerve sheath tumors. MRI characteristics could distinguish MPNST by the absence of a target sign, ill-defined margins and perilesional edema. FDG-PET had the highest diagnostic accuracy in neurofibromatosis type 1 patients, efficacious wen using SUVmax or T/L ratio. Personal remarks: A reasonable number of studies was reviewed, using also individual patient data. Several subgroup analyses have been performed to assess sources of hetereogeneiety. QUADAS-2 was used as a tool to assess methodologic quality and risk of bias, and applicability. Level of evidence:

	U: Karabatsou, 2009 V: Karsy, 2016 W: Lerman, 2019 X: Li, 2008 Y: Matsumine, 2008 Z: Matsumoto, 2015 AA: Mautner, 2007 AB: Meany, 2013 AC: Moharir, 2010 AD: Nose, 2013 AE: Park, 2013 AF: Razek, 2018 AG: Reinert, 2018 AH: Salamon, 2013 AI: Salamon, 2014 AK: Salamon, 2015 AL: Schwabe, 2019 AM: Tsai, 2012 AN: Van der Gucht, 2016 AO: Warbey, 2009 AP: Wasa, 2010 AQ: Well, 2018 AR: Yu, 2016 <u>Study design</u>: All: cohort studies <u>Setting and Country</u>: Not reported <u>Funding and conflicts of interest</u> All: not reported	<u>N, mean age</u> A: 42; 40 (8 to 68) B: 21; 30 (8 to 53) C: 41; 14 (3 to 23) D: 38; 31 (7 to 77) E: 34; 46 (21 to 82) F: 45; 37 (17 to 73) G: 38; 38 (16 to 79) H: 13; 45 (18 to 81) I: 56; 50 (15 to 92) J: 41; 36 (8 to 77) K: 113; 31 (2 to 77) L: 54; 35 (9 to 86) M: 29; 38 (18 to 54) N: 31; 30 (2 to 63) O: 20; 42 (11 to 78) P: 18; 24 (12 to 62) Q: 105; 31 (5 to 71) R: 30; 43 (3 to 87) S: 32; 21 (5 to 50) T: 124; 36 (12 to 69) U: 9; 38 (19 to 63) V: 127; 41 (na) W: 17; 35 (15 to 73) X: 26; 47 (20 to 82) Y: 37; 43 (14 to 80) Z: 23; 43 (2 to 71)	T: U: V: T1-weighted, and T2-weighted MRI W: X: T1-weighted, and T2-weighted MRI Y: T1-weighted, and T2-weighted MRI Z: T1-weighted, and T2-weighted MRI AA: AB: AC: AD: AE: AF: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI AG: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI AH: AI: AK: AL: T1-weighted, and T2-weighted MRI AM: AN: AO: AP: T1-weighted, and T2-weighted MRI AQ: diffusion weighted imaging (DWI), T1-weighted, and T2-weighted MRI AR: T1-weighted, and T2-weighted MRI	AG: PET-CT AH: PET-CT AI: PET-CT AK: PET-CT AL: PET-CT AM: PET-CT AN: PET-CT AO: PET-CT AP: AQ: AR:		ratio: 0.38 (95% CI: 0.12 to 0.69) <u>Outcome measure-3 Pooled</u> FDR-PET D: SUVmax sensitivity (median cutoff 3.96, IQR 2.35 to 6.1) IR: 0.94 (95% CI: 0.91 to 0.97) D: SUVmax specificity: 0.81 (95% CI: 0.76 to 0.87) D: SUVmax +LR: 5.22 (95% CI: 3.74 to 7.51) D: SUVmax -LR: 0.07 (95% CI: 0.03 to 0.12) <u>Outcome measure-4 Pooled</u> FDR-PET E: Tumor-to-liver ratio sensitvity (median cutoff 1.77, IQR 1.38 to 3.0): 0.93 (95% CI: 0.87 to 0.97) E: Tumor-to-liver ratio specificity: 0.79 (95% CI: 0.70 to 0.86) E: Tumor-to-liver ratio +LR: 4.69 (95% CI: 2.89 to 7.41) E: Tumor-to-liver ratio -LR: 0.09 (95% CI: 0.03 to 0.18) <u>Outcome measure-5 Pooled</u> FDR-PET F: Qualitative assessment sensitivity: 0.94 (95% CI: 0.88 to 0.98) F: Qualitative assessment specificity: 0.82 (95% CI: 0.71 to 0.91) F: Qualitative assessment +LR: 5.86 (95% CI: 3.00 to 11.24)	MRI: Low (high risk of bias: -2) PET-CT: Low (high risk of bias: -2)

		AA: 4; 25.5 (8 to 47) AB: 14; 18 (10 to 45) AC: 11; 9 (2 to 14) AD: NA; 52 (15 to 88) AE: 104; 33 (14 to 63) AF: 34; 34 (9 to 64) AG: 28; 20 (2 to 44) AH: 50; 33 (2 to 69) AI: 49; 33 (2 to 69) AK: 36; 37 (17 to 69) AL: 41; 30 (9 to 62) AM: 18; 15 (1 to 20) AN: 49; 33 (na) AO: 62; 31 (9 to 86) AP: 61; 42 (16 to 83) AQ: 26; 34 (17 to 54) AR: 34; 53 (23 to 78) <u>*Sex*</u>*:* *All: I: not reported%; C: not reported%* Groups comparable at baseline? Not applicable				F: Qualitative assessment - LR: 0.07 (95% CI: 0.02 to 0.16)	

Risk of bias table

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Dubreuil, 2017	Yes	Yes	No (only discription of included studies)	No (no extensive description)	Not applicable	Yes (PRISMA)	Yes	No	No
Martin, 2020	Yes	Yes	No (only description of included studies)	Yes	Not applicable	Yes (QUADAS-2)	Yes	No	No

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a “yes,” source of funding or support must be indicated for the systematic review AND for each of the included studies.

Table of excluded studies

Reference	Reason for exclusion
Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. Lancet Oncol. 2009 Dec;10(12):1188-98. doi: 10.1016/S1470-2045(09)70226-8. PMID: 19959075.	wrong study design: review without systematic search
Annual Scientific Meeting Abstracts of the European Society of Musculoskeletal Radiology (ESSR) 2018, Amsterdam, The Netherlands. Skeletal Radiol. 2018 Mar 7:895-909. doi: 10.1007/s00256-018-2924-6. Epub ahead of print. PMID: 29511790.	wrong publication type: conference abstract
Arkader A, Dormans JP. Pediatric extremity soft-tissue sarcomas: from diagnosis to surgical treatment. Current Orthopaedic Practice. 2010; 21 (5): 508-517. doi: 10.1097/BCO.0b013e3181e575bf.	wrong study design: review without systematic search
Boriani F, Raposio E, Errani C. Imaging Features of Primary Tumors of the Hand. Curr Med Imaging. 2021;17(2):179-196. doi: 10.2174/1573405616999200817173154. PMID: 32811403.	wrong study design: review without systematic search
Chen, PH., Mankoff, D.A. & Sebro, R.A. Clinical overview of the current state and future applications of positron emission tomography in bone and soft tissue sarcoma. Clin Transl Imaging 5, 343–358 (2017). doi: 10.1007/s40336-017-0236-9	wrong study design: review without systematic search
Crombé A, Fadli D, Italiano A, Saut O, Buy X, Kind M. Systematic review of sarcomas radiomics studies: Bridging the gap between concepts and clinical applications? Eur J Radiol. 2020 Nov;132:109283. doi: 10.1016/j.ejrad.2020.109283. Epub 2020 Sep 12. PMID: 32980727.	wrong outcome
Edem I, DeMonte F, Raza SM. Advances in the management of primary bone sarcomas of the skull base. J Neurooncol. 2020 Dec;150(3):393-403. doi: 10.1007/s11060-020-03497-6. Epub 2020 Apr 18. PMID: 32306199.	wrong type of tumor (bone sarcomas)
Favinger JL, Hippe DS, Davidson DJ, Elojeimy S, Roth ES, Lindberg AW, Ha AS. Soft Tissue Sarcoma Response to Two Cycles of Neoadjuvant Chemotherapy: A Multireader Analysis of MRI Findings and Agreement with RECIST Criteria and Change in SUVmax. Acad Radiol. 2018 Apr;25(4):470-475. doi: 10.1016/j.acra.2017.10.013. Epub 2017 Dec 19. PMID: 29273189.	wrong intervention: chemotherapy
Gitto S, Cuocolo R, Albano D, Morelli F, Pescatori LC, Messina C, Imbriaco M, Sconfienza LM. CT and MRI radiomics of bone and soft-tissue sarcomas: a systematic review of reproducibility and validation strategies. Insights Imaging. 2021 Jun 2;12(1):68. doi: 10.1186/s13244-021-01008-3. PMID: 34076740; PMCID: PMC8172744.	wrong outcome
Gong LH, Liu WF, Ding Y, Geng YH, Sun XQ, Huang XY. Diagnosis and Differential Diagnosis of Desmoplastic Fibroblastoma by Clinical, Radiological, and Histopathological Analyses. Chin Med J (Engl). 2018 Jan 5;131(1):32-36. doi: 10.4103/0366-6999.221274. PMID: 29271377; PMCID: PMC5754955.	wrong study design: case series
Gruber L, Gruber H, Luger AK, Glodny B, Henninger B, Loizides A. Diagnostic hierarchy of radiological features in soft tissue tumours and proposition of a simple diagnostic	wrong intervention

algorithm to estimate malignant potential of an unknown mass. Eur J Radiol. 2017 Oct;95:102-110. doi: 10.1016/j.ejrad.2017.07.020. Epub 2017 Jul 28. PMID: 28987653.	
Hamza A, Gidley PW, Learned KO, Hanna EY, Bell D. Uncommon tumors of temporomandibular joint: An institutional experience and review. Head Neck. 2020 Aug;42(8):1859-1873. doi: 10.1002/hed.26106. Epub 2020 Feb 10. PMID: 32040228.	wrong publication type: institutional experience and review without systematic search
Huang YT, Huang YL, Ng KK, Lin G. Current Status of Magnetic Resonance Imaging in Patients with Malignant Uterine Neoplasms: A Review. Korean J Radiol. 2019 Jan;20(1):18-33. doi: 10.3348/kjr.2018.0090. Epub 2018 Dec 27. PMID: 30627019; PMCID: PMC6315066.	wrong study design: review without systematic search
Köhler G, Vollmer M, Nath N, Hessler PA, Dennis K, Lehr A, Köller M, Riechmann C, Bralo H, Trojnarska D, Lehnhoff H, Krichbaum J, Krichbaum M, Evert K, Evert M, Zygmunt M, Kaderali L. Benign uterine mass-discrimination from leiomyosarcoma by a preoperative risk score: a multicenter cohort study. Arch Gynecol Obstet. 2019 Dec;300(6):1719-1727. doi: 10.1007/s00404-019-05344-0. Epub 2019 Nov 1. PMID: 31677088.	wrong intervention
Lai CH, Lin G, Yen TC, Liu FY. Molecular imaging in the management of gynecologic malignancies. Gynecol Oncol. 2014 Oct;135(1):156-62. doi: 10.1016/j.ygyno.2014.07.092. Epub 2014 Jul 24. PMID: 25065896.	wrong population
Luna R, Fayad LM, Rodriguez FJ, Ahlawat S. Imaging of non-neurogenic peripheral nerve malignancy-a case series and systematic review. Skeletal Radiol. 2021 Jan;50(1):201-215. doi: 10.1007/s00256-020-03556-z. Epub 2020 Jul 23. PMID: 32699955.	wrong study design: SR of cases
Lunn BW, Littrell LA, Wenger DE, Broski SM. 18F-FDG PET/CT and MRI features of myxoid liposarcomas and intramuscular myxomas. Skeletal Radiol. 2018 Dec;47(12):1641-1650. doi: 10.1007/s00256-018-3000-y. Epub 2018 Jun 20. PMID: 29926115.	wrong study design: case series
Mahmood U, Nguyen JD, Chang J, Gu M, Wong BJ. Atypical lipomatous tumor/well-differentiated liposarcoma of the parotid gland: case report and literature review. Ear Nose Throat J. 2009 Oct;88(10):E10-6. PMID: 19826985.	wrong study design: case report and literature review
Sun C, Zou J, Wang Q, Wang Q, Han L, Batchu N, Ulain Q, Du J, Lv S, Song Q, Li Q. Review of the pathophysiology, diagnosis, and therapy of vulvar leiomyoma, a rare gynecological tumor. J Int Med Res. 2018 Feb;46(2):663-674. doi: 10.1177/0300060517721796. Epub 2017 Sep 6. PMID: 28875758; PMCID: PMC5971502.	wrong study design: review without systematic search
Surov A, Gottschling S, Wienke A, Meyer HJ, Spielmann RP, Dralle H. Primary Thyroid Sarcoma: A Systematic Review. Anticancer Res. 2015 Oct;35(10):5185-91. PMID: 26408676.	wrong study design: SR of cases
Uhlig J, Uhlig A, Bachanek S, Onur MR, Kinner S, Geisel D, Köhler M, Preibsch H, Puesken M, Schramm D, May M, De Visschere P, Weber MA, Surov A. Primary renal sarcomas: imaging features and discrimination from non-sarcoma renal tumors. Eur Radiol. 2022 Feb;32(2):981-989. doi: 10.1007/s00330-021-08201-4. Epub 2021 Jul 31. PMID: 34331576; PMCID: PMC8794936.	wrong intervention

Vijay A, Ram L. Retroperitoneal liposarcoma: a comprehensive review. Am J Clin Oncol. 2015 Apr;38(2):213-9. doi: 10.1097/COC.0b013e31829b5667. PMID: 24136142.	wrong study design: review without systematic search
Wang JG, Cui L, Jiang T, Li YJ, Wei ZM. Primary cardiac leiomyosarcoma: an analysis of clinical characteristics and outcome patterns. Asian Cardiovasc Thorac Ann. 2015 Jun;23(5):623-30. doi: 10.1177/0218492315574197. Epub 2015 Mar 3. PMID: 25740020.	wrong study design: case series
Wen KC, Horng HC, Wang PH, Chen YJ, Yen MS, Ng HT; Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma Part I-Uterine leiomyosarcoma: The Topic Advisory Group systematic review. Taiwan J Obstet Gynecol. 2016 Aug;55(4):463-71. doi: 10.1016/j.tjog.2016.04.033. PMID: 27590365.	wrong study design: review without systematic search
Wienbeck S, Meyer HJ, Herzog A, Nemat S, Teifke A, Heindel W, Schäfer F, Kinner S, Müller-Schimpfle M, Surov A. Imaging findings of primary breast sarcoma: Results of a first multicenter study. Eur J Radiol. 2017 Mar;88:1-7. doi: 10.1016/j.ejrad.2016.12.020. Epub 2016 Dec 21. PMID: 28189193.	wrong study design: case series

Zoekverantwoording

Algemene informatie

Richtlijn: NVVH - wekedelentumoren	
Uitgangsvraag: Wat is het optimale beeldvormend onderzoek dat gedaan moet worden bij patiënten met verdenking op wekedelensarcomen?	
Database(s): Ovid/Medline, Embase	Datum:20-9-2022
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Soft tissue sarcoma AND (CT OR ultrasound) AND MRI AND diagnostisch filter Van de sleutelartikelen wordt alleen de studie van Noebauer gevonden omdat: De artikelen van Kwee en Weis alleen spreken over MRI in titel, abstract en indexterm en geen CT of ultrasound Het artikel Amini geïndexeerd is diagnostic imaging MRI niet als CT of ultrasound Het artikel van Mcaddy alleen CT benoemt in titel, abstract en indexterm en geen MRI Het artikel van Styring een richtlijn betreft waarin niet specifiek beeldvorming wordt benoemd in title, abstract, indexterm.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 20-9-2022 met relevante zoektermen gezocht vanaf 2010 naar SRs, RCTs en observationele studies over het optimale beeldvormend onderzoek dat gedaan moet worden bij patiënten met verdenking op wekedelensarcomen. De literatuurzoekactie leverde 789 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	67	17	74
RCTs	15	6	18
Observationele studies	438	380	697
Overig			
Totaal			789

Zoekstrategie

Embase

No.	Query	Results
#26	#24 NOT #25 Overige sleutelartikelen niet gevonden	5
#25	#17 AND #24 Sleutelartikel Noebauer gevonden	1
#24	#18 OR #19 OR #20 OR #21 OR #22 OR #23 Sleutelartikelen	6
#23	simple AND for AND efficient AND 'soft tissue' AND sarcomas AND a AND 'population based' AND evaluation AND of AND adherence AND to AND guidelines AND referral AND patterns	1
#22	musculoskeletal AND 'soft tissue' AND sarcoma AND quality AND assessment AND of AND initial AND mri AND reports AND shows AND frequent AND deviation AND from AND essr AND guidelines	1
#21	soft AND tissue AND tumors AND in AND adults AND 'essr approved' AND guidelines AND for AND diagnostic AND imaging	2
#20	contrast AND agents AND improve AND detection AND of AND recurrent AND 'soft tissue' AND sarcoma AND at AND mri	1
#19	ct AND imaging AND improves AND histopathological AND grading AND of AND retroperitoneal AND leiomyosarcomas.	1
#18	diagnostic AND performance AND of AND mri AND in AND detecting AND locally AND recurrent AND soft AND tissue AND sarcoma AND systematic AND review AND 'meta analysis'	1
#17	#14 OR #15 OR #16	493
#16	#9 AND (#12 OR #13) OBS	438
#15	#9 AND #11 RCT	15
#14	#9 AND #10 SR	67

No.	Query	Results
#13	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13457242
#12	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#11	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814

No.	Query	Results
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#9	#7 AND #8	1496
#8	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	9383311
#7	#6 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	4343
#6	#1 AND #4 AND #5	7550
#5	#2 OR #3	2636231
#4	'nuclear magnetic resonance imaging'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti	1441067

No.	Query	Results
#3	'echography'/exp OR 'color doppler flowmetry'/exp OR ultraso*:ab,ti,kw OR sonograph*:ab,ti,kw OR echograph*:ab,ti,kw OR echotomograph*:ab,ti,kw OR ((colo?r NEAR/3 doppler):ti,ab,kw)	1304295
#2	'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	1589128
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 (sarcoma* OR tumor* OR tumour* OR neoplasm* OR cancer*)):ti,ab,kw)	96757

Ovid/Medline

#	Searches	Results
19	17 not 16 not 15 OBS	380
18	16 not 15 RCT	6
17	8 and (13 or 14)	393
16	10 and 11	7
15	10 and 12 SR	17
14	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair	5250961

	or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
13	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4250801
12	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	619051
11	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1547491
10	8 and 9	582
9	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	7532678
8	7 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1495
7	limit 6 to yr="2010 -Current"	1529
6	1 and 4 and 5	2684
5	2 or 3	1434873

4	exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	907609
3	exp Ultrasonography/ or ultraso*.ti,ab,kf. or sonograph*.ti,ab,kf. or echograph*.ti,ab,kf. or echotomograph*.ti,ab,kf. or ((color or colour) adj3 doppler).ti,ab,kf.	719044
2	exp Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf.	809827
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf.	61659

Module 2 – Beeldvorming stadiëring

Search and select
A systematic review of the literature was performed to answer the following question:
What is the optimal imaging protocol for staging in patients with a soft tissue sarcoma?

PICO 1
Population: patients with (suspected) soft tissue sarcoma
Index test: computed tomography (CT) chest
Comparator: CT chest/abdomen/pelvis
Reference: clinical course
Outcomes: diagnostic accuracy of CT chest vs CT chest/abdomen/pelvis in optimal staging of sarcomas (per histological type and grade)
Timing/setting: moment of diagnosis and in follow up

PICO 2
Population: patients with (suspected) soft tissue sarcoma
Index test: CT chest
Comparator: chest X-ray
Reference: clinical course
Outcomes: diagnostic accuracy of CT chest vs chest X-ray in optimal staging of sarcomas (per histological type and grade)
Timing/setting: moment of diagnosis and in follow-up

Relevant outcome measures
A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until December 2, 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 192 hits. Studies were selected based on the following criteria: fit PICO, systematic reviews, randomized controlled trials, observational studies, article in English or Dutch, published after 2004. 20 studies were initially selected based on title and abstract screening. After reading the full text, 18 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results
Two (2) studies were included in the analysis of the literature that fit PICO 2 (CT chest versus chest X-ray). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables. Zero (0) studies were included that fit PICO 1 (CT chest versus CT chest/abdomen/pelvis).

Summary of literature
Description of studies
Christie-Large (2008) retrospectively reviewed charts of 1170 patients (age range: 3-94 years) with newly diagnosed soft tissue sarcoma (STS) from the database of a tertiary referral center in Birmingham, the United Kingdom, to determine the presence of lung metastases at presentation. In all patients, a chest computed tomography (CT) and chest X-ray were performed. The reference test (thoracotomy or progression on subsequent CT) was only

performed in patients with a lung metastasis found on chest CT. Among 92 patients with proven lung metastases (7.9%), survival data were available.

Ferrari (2012) retrospectively reviewed charts of 258 previously untreated children and adolescents (0-21 years) with a diagnosis of synovial sarcoma (SS) from several databases of European pediatric groups to determine the rate of lung metastases. Chest CT scans were presumably performed in all patients, while a chest X-ray was only performed in patients with lung metastases according to chest CT (n=10; 3.9%). A reference test was not reported. Diagnostic accuracy measures of chest X-ray were calculated by the guideline author, using chest CT as reference test. Data on clinical outcomes were not reported.

Results

Soft tissue sarcoma

Diagnostic accuracy

Chest CT

Christie-Large (2008) reported on diagnostic accuracy measures of chest CT for the detection of lung metastases in patients with a new diagnosis of soft tissue sarcoma. For these measures, they used thoracotomy or progression on subsequent CT as the reference standard.

Accuracy

Christie-Large (2008) reported an accuracy of 99.7% (95% CI 99.1-99.9%) to detect lung metastases.

Sensitivity

Christie-Large (2008) reported a sensitivity of 100% (95% CI 96.7-100%) to detect lung metastases.

Specificity

Christie-Large (2008) reported a specificity of 99.6% (95% CI 99.1-99.9%) to detect lung metastases.

Positive predictive value (PPV)

Christie-Large (2008) reported a PPV of 95.8% (95% CI 89.7-98.9%) to detect lung metastases.

Negative predictive value (NPV)

Christie-Large (2008) reported a NPV of 100% (95% CI 99.7-100%) to detect lung metastases.

Chest X-ray

Christie-Large (2008) reported on diagnostic accuracy measures of chest X-ray for the detection of lung metastases in patients with new diagnosis of soft tissue sarcoma. For these measures, they used chest CT as the reference standard. They also reported numbers of lung metastases found by both chest CT and chest X-ray per stage (or subgroup of patients), according to the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system assuming there were no metastases identified. Since these numbers per stage were too small for meaningful interpretation, we did not calculate the diagnostic accuracy measures per stage.

Accuracy

Christie-Large (2008) reported an accuracy of 99.7% (95% CI 99.1-99.9%) to detect lung metastases.

Sensitivity
Christie-Large (2008) reported a sensitivity of 60.9% (95% CI 50.1-70.9%) to detect lung metastases.

Specificity
Christie-Large (2008) reported a specificity of 99.6% (95% CI 99.1-99.9%) to detect lung metastases.

Positive predictive value (PPV)
Christie-Large (2008) reported a PPV of 93.3% (95% CI 83.8-98.2%) to detect lung metastases.

Negative predictive value (NPV)
Christie-Large (2008) reported a NPV of 96.8% (95% CI 95.5-97.7%) to detect lung metastases.

Survival
Christie-Large 2008 reported on survival among 92 patients with proven lung metastases. They compared survival among patients whose metastases were visible on both chest CT and chest X-ray with patients whose metastases were only visible on chest CT. Median survival among patients whose metastases were visible on both chest CT and chest X-ray was 10 months. Median survival among patients whose metastases were only visible on chest CT was 14 months. This difference was not statistically significant (p=0.21). The authors did not report a (standardized) mean difference.

Synovial sarcoma
Diagnostic accuracy
Chest X-ray
Ferrari (2012) reported on diagnostic accuracy measures of chest X-ray for the detection of lung metastases in patients with a new diagnosis of synovial sarcoma. For these measures, they used chest CT as the reference standard.

Accuracy
Ferrari (2012) reported an accuracy of 99.6% (95% CI 97.9-100%) to detect lung metastases.

Sensitivity
Ferrari (2012) reported a sensitivity of 90.0% (95% CI 55.5-99.8%) to detect lung metastases.

Specificity
Ferrari (2012) reported a specificity of 100% (95% CI 98.5-100%) to detect lung metastases.

Positive predictive value (PPV)
Ferrari (2012) reported a PPV of 100% (95% CI 66.4-100%) to detect lung metastases.

Negative predictive value (NPV)
Ferrari (2012) reported a NPV of 99.6% (95% CI 97.8-100%) to detect lung metastases.

Risk of bias
For some components, the risk of bias was considered high, including patient flow and timing (Christie-Large 2008, Ferrari 2012) and the reference standard (Ferrari 2012).

Level of evidence of the literature
Soft tissue sarcoma

Diagnostic accuracy

Chest CT

The level of evidence regarding the accuracy started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the sensitivity started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the specificity started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the PPV started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the NPV started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

Chest X-ray

The level of evidence regarding the accuracy started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the sensitivity started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the specificity started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the PPV started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias)and applicability (bias due to indirectness).

The level of evidence regarding the NPV started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

Survival

The level of evidence regarding the survival started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and number of included patients (imprecision).

Synovial sarcoma

Diagnostic accuracy

Chest X-ray

The level of evidence regarding the accuracy started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the sensitivity started as High (diagnostic accuracy studies) and was downgraded by three levels to Very low because of study limitations (risk of bias), applicability (bias due to indirectness), and number of included patients (imprecision).

The level of evidence regarding the specificity started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

The level of evidence regarding the PPV started as High (diagnostic accuracy studies) and was downgraded by three levels to Very low because of study limitations (risk of bias), applicability (bias due to indirectness), and number of included patients (imprecision).

The level of evidence regarding the NPV started as High (diagnostic accuracy studies) and was downgraded by two levels to Low because of study limitations (risk of bias) and applicability (bias due to indirectness).

Conclusions

Soft tissue sarcoma

Low GRADE	The evidence suggests that the chest CT has a high accuracy, high sensitivity, high specificity, high positive predictive value, and high negative predictive value in the detection of lung metastases in patients with soft tissue sarcoma. *Source: Christie-Large, 2008*
Low GRADE	The evidence suggests that the chest X-ray has a high accuracy, reasonable sensitivity, high specificity, high positive predictive value, and high negative predictive value in the detection of lung metastases in patients with soft tissue sarcoma. *Source: Christie-Large, 2008*
Low GRADE	The evidence suggests that the use of chest CT for the detection of lung metastases results in little to no difference in survival compared to chest X-ray in patients with soft tissue sarcoma. *Source: Christie-Large, 2008*

Synovial sarcoma

Low GRADE	The evidence suggests that the chest X-ray has a high accuracy, high specificity, high positive predictive value, and high negative predictive value in the detection of lung metastases in patients with synovial sarcoma. *Source: Ferrari, 2012*
Very low GRADE	The evidence is very uncertain about the sensitivity of chest X-ray in the detection of lung metastases in patients with synovial sarcoma. *Source: Ferrari, 2012*

Kennislacunes

What is the optimal imaging protocol for staging in patients with soft tissue sarcoma?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
alle	1-3	Minimaal, geen nieuwe modaliteiten voorgesteld	-	-	geen	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Research question: What is the most optimal imaging procedure for staging in patients with (suspected) soft tissue sarcomas? (PICO 2: chest CT versus chest X-ray)

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Christie-Large, 2008	Type of study: retrospective study Setting and country: tertiary referral center, UK Funding and conflicts of interest: funding was not reported; no conflicts of interest declared	Inclusion criteria: new diagnosis of soft tissue sarcoma between 1996 and mid 2004 Exclusion criteria: NR N=1170 Prevalence of lung metastases at diagnosis: 7.9% Median age: 46 years (range: 3-94 years) Sex: NR Other important characteristics: most common diagnoses were pleomorphic sarcoma (20.1%), liposarcoma (13.6%), leiomyosarcoma	Index test: chest CT Cut-off point(s): NA Comparator test: chest X-ray Cut-off point(s): NA	Describe reference test: thoracotomy or progression on subsequent CT Cut-off point(s): NA	Time between the index test and reference test: NR For how many participants were no complete outcome data available? All 92 patients with proven lung metastases had outcome data (survival) available Reasons for incomplete outcome data described?: NA	**Diagnostic accuracy** <u>Chest CT</u> Accuracy: 99.7% (95% CI 99.1-99.9%) Sensitivity: 100% (95% CI 96.7-100%) Specificity: 99.6% (95% CI 99.1-99.9%) PPV: 95.8% (95% CI 89.7-98.9%) NPV: 100% (95% CI 99.7-100%) <u>Chest X-ray</u> Accuracy: 96.6% (95% CI 95.4-97.5%) Sensitivity: 60.9% (95% CI 50.1-70.9%) Specificity: 99.6% (95% CI 99.1-99.9%) PPV: 93.3% (95% CI 83.8-98.2%) NPV: 96.8% (95% CI 95.5-97.7%) **Survival (n=92)** <u>Overall</u> Median survival: 11 months 24% survival at 2 years 11% survival at 5 years <u>Chest CT</u> Median survival: 10 months	The authors propose that all patients with a suspected soft tissue sarcoma have a chest X-ray. Patients should only routinely undergo a chest CT if an abnormality has been observed on chest X-ray or in case of high/intermediate grade, deep tumours >5 cm (stage 2b/3). <u>Personal notes</u> The authors reported that the prevalence of lung metastases was 8.2% but this includes 4 cases who later turned out to have benign lung lesions. Very short description of methods section. It is unclear whether all patients received the reference test. Sensitivity and NPV for chest CT should thus be interpreted with caution, as patients without lung metastases on chest CT may not have been

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
		(11.7%), malignant peripheral nerve sheath tumour (9%) and synovial sarcoma (10.2%). T1 (≤5 cm): 31.4% T2 (>5 cm): 68.6%				<u>Chest X-ray</u> Median survival: 14 months P-value for difference in survival between chest CT and chest X-ray: 0.21	confirmed by a reference test. Diagnostic accuracy measures of chest X-ray were calculated using chest CT as reference test. 95% CIs were calculated by the guideline author.
Ferrari, 2012	Type of study: retrospective study Setting and country: databases of different European paediatric groups Funding and conflicts of interest: funding was not reported; no conflicts of interest declared	Inclusion criteria: (1) study period: 1988–2005; (2) patient's age 0–21 years; (3) histological diagnosis of synovial sarcoma; (4) all tumour sites; (5) no pre-treatment (apart from initial resection) Exclusion criteria: NR N=258	Describe index test: chest CT Cut-off point(s): NA Comparator test: chest X-ray Cut-off point(s): NA	Describe reference test: NR Cut-off point(s): NA	Time between the index test and reference test: NR For how many participants were no complete outcome data available? No outcome data available for all patients Reasons for incomplete outcome data described? Not considered	**Diagnostic accuracy** <u>Chest X-ray</u> Accuracy: 99.6% (95% CI 97.9-100%) Sensitivity: 90.0% (95% CI 55.5-99.8%) Specificity: 100% (95% CI 98.5-100%) PPV: 100% (95% CI 66.4-100%) NPV: 99.6% (95% CI 97.8-100%)	The authors assumed that all patients underwent chest CT scanning according to protocol, but they could not definitely confirm this. The authors suggest that a chest X-ray for pulmonary staging purposes suffices for patients with a tumour <5 cm. A chest CT should be performed in patients with suspicious radiological findings. Among patients with tumours >5 cm, a chest CT was considered necessary. <u>Personal notes</u> Diagnostic accuracy measures of chest X-ray (including 95% CIs) were

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
		Prevalence of lung metastases: 3.9% Age: <10 years: 26.7% ≥10 years: 73.3% Sex: 59.3% M / 40.7% F Other important characteristics: T1A: 36.4% T1B: 17.1% T2A: 11.6% T2B: 34.9% N0: 47.7% N1: 2.3% Nx: 50.0%					calculated by the guideline author, using chest CT as reference test. It was not described how many patients had available data on chest CT. Thus, sensitivity and NPV for chest X-ray should be interpreted with caution.

CI, confidence interval; CT, computed tomography; NA, not applicable; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

Risk of bias table

Research question: What is the most optimal imaging procedure for staging in patients with (suspected) soft tissue sarcomas? (PICO 2: chest CT versus chest X-ray)

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Christie-Large, 2008	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? NA	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No	Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Unclear Did patients receive the same reference standard? No Were all patients included in the analysis? No	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	
Ferrari, 2012	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear	Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? NA	Is the reference standard likely to correctly classify the target condition? No Were the reference standard results interpreted without knowledge of the results of the index test? No	Was there an appropriate interval between index test(s) and reference standard? No Did all patients receive a reference standard? No Did patients receive the same reference standard?	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
				No Were all patients included in the analysis? No	Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: HIGH**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	

Table of excluded studies

Reference	Reason for exclusion
Annovazzi A, Rea S, Zoccali C, et al. Diagnostic and clinical impact of 18f-FDG PET/CT in staging and restaging soft-tissue sarcomas of the extremities and trunk: Mono-institutional retrospective study of a sarcoma referral center, 2020; Journal of Clinical Medicine.	Wrong comparison
De Angelis F, Guy F, Bertaut A, et al. Limbs and trunk soft tissue sarcoma systematic local and remote monitoring by MRI and thoraco-abdomino-pelvic scanner: A single-centre retrospective study, 2019; European Journal of Surgical Oncology.	Wrong comparison, wrong population (operated patients)
Durr H, Rauh J, Baur-Melnyk A, et al. Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients, 2018; BMC Cancer.	No comparison
Hagi T, Nakamura T, Sugino Y, et al. Is FDG-PET/CT useful for diagnosing pulmonary metastasis in patients with soft tissue sarcoma?, 2018; Anticancer Research.	Wrong comparison
Iagaru A, Chawla S, Menendez L, and Conti P. 18F-FDG PET and PET/CT for detection of pulmonary metastases from musculoskeletal sarcomas, 2006; Nuclear Medicine Communications.	Wrong comparison
Iagaru A, Quon A, McDougall I, and Gambhir S. F-18 FDG PET/CT evaluation of osseous and soft tissue sarcomas, 2006; Clinical Nuclear Medicine.	Wrong comparison
Kogay M, Thariat J, Benisvy D, et al. Is FDG TEP CT practice changing in the management of sarcomas in adults?, 2016; Bulletin du Cancer.	Not available
Mayo Z, Kennedy S, Gao Y, and Miller B. What Is the Clinical Importance of Incidental Findings on Staging CT Scans in Patients With Sarcoma?, 2019; Clinical Orthopaedics and Related Research.	No comparison
Miller B, Carmody Soni E, Reith J, et al. CT scans for pulmonary surveillance may be overused in lower-grade sarcoma, 2012; The Iowa Orthopaedic Journal.	Wrong comparison, wrong population (operated patients)
Nishiyama Y, Tateishi U, Kawai A, et al. Prediction of treatment outcomes in patients with chest wall sarcoma: Evaluation with PET/CT, 2012; Japanese Journal of Clinical Oncology.	No comparison
Roberge D, Hickeson M, Charest M, and Turcotte RE. Initial McGill experience with fluorodeoxyglucose PET/CT staging of soft-tissue sarcoma, 2010; Current Oncology.	Wrong comparison
Roberge D, Vakilian S, Alabed Y, et al. FDG PET/CT in initial staging of adult soft-tissue sarcoma, 2012; Sarcoma.	Wrong comparison
Saifuddin A, Shaheer M, Dalal P, and Strauss S. The diagnosis of pulmonary metastases on chest computed tomography in primary bone sarcoma and musculoskeletal soft tissue sarcoma, 2021; British Journal of Radiology.	Wrong study design (narrative review)
Singh T, Sharma A, Sharma A, et al. Utility of 18F-FDG-PET/CT in management and prognostication of treatment naïve late-stage soft tissue sarcomas, 2021; Nuclear Medicine Communications.	No comparison
Tateishi U, Yamaguchi U, Maeda T, et al. Staging performance of carbon-11 choline positron emission tomography/ computed	Wrong comparison

tomography in patients with bone and soft tissue sarcoma: Comparison with conventional imaging, 2006; Cancer Science.	
Tateishi U, Yamaguchi U, Seki K, et al. Bone and soft-tissue sarcoma: Preoperative staging with fluorine 18 fluorodeoxyglucose PET/CT and conventional imaging, 2007; Radiology.	Wrong comparison
Tsoi K, Lowe M, Tsuda Y, et al. How Are Indeterminate Pulmonary Nodules at Diagnosis Associated with Survival in Patients with High-Grade Osteosarcoma?, 2021; Clinical Orthopaedics and Related Research.	Wrong population (osteosarcoma or spindle cell sarcoma of bone)
Vaarwerk B, Bisogno G, McHugh K, et al. Indeterminate Pulmonary Nodules at Diagnosis in Rhabdomyosarcoma: Are They Clinically Significant? A Report From the European Paediatric Soft Tissue Sarcoma Study Group, 2019; Journal of Clinical Oncology.	Wrong comparison

Zoekverantwoording

Algemene informatie

Richtlijn: NVVH - Wekedelentumoren	
Uitgangsvraag: UV2 Wat is het optimale beeldvormend onderzoek voor de stadiëring bij patiënten met verdenking op wekedelen tumoren/sarcomen?	
Database(s): Ovid/Medline, Embase	Datum:2-12-2022
Periode: 2005-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Soft tissue sarcoma AND Chest CT AND sensitiviteit, specificiteit Van de sleutelartikelen worden er drie niet gevonden: 1. Soft Tissue and Visceral Sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. A. Gronchi, A.B. Miah, A.P. Dei Tos et al. Published in 2021 - Ann Oncol (2021). Geen abstract, algemeen richtlijn geen specifieke trefwoorden 2. Whole-body magnetic resonance imaging in myxoid liposarcoma: A useful adjunct for the detection of extra-pulmonary metastatic disease. Eur J Surg Oncol. 2016 Apr;42(4):574-80. doi: 10.1016/j.ejso.2015.12.011. Epub 2016 Jan 13 Geen terminologie voor sensitiviteit en specificiteit 3. Sheikhbahaei S., Marcus C., Hafezi-Nejad N., Taghipour M., Subramaniam R.M. Value of FDG PET/CT in Patient Management and Outcome of Skeletal and Soft Tissue Sarcomas. PET Clin. 2015;10:375–393. doi: 10.1016/j.cpet.2015.03.003. Geen terminologie voor chest ct Mailwisseling:	

Dank voor de duidelijke toelichting van de strategieën.
We hebben de opties besproken en je kunt de search uitvoeren volgens strategie 2, gefocust op STS en CT Thorax.
Met vriendelijke groet,

dr. Linda M.P. Wesselman
Adviseur

Onderwerp: Re: Richtlijn Wekedelentumoren - zoekformulier UV 2 beeldvorming stadiëring
Hoi Linda,
Naar aanleiding van jouw vragen heb ik verschillende zoekstrategieën opgezet:

1. Soft tissue sarcoma EN CT EN cancer staging (228 diagnostische studies SR + observationeel 1 database)
2. Soft tissue sarcoma EN CT thorax (127 diagnostische studies SR + observationeel 1 database)

Met de eerste strategie worden 3 van de 4 sleutelartikelen gevonden. De richtlijn wordt niet gevonden, omdat deze geen abstract heeft en in de indextermen alleen gesproken wordt over soft tissue sarcoma. De richtlijn wordt ook in de tweede strategie niet gevonden.
Met de tweede strategie wordt het sleutelartikel: Sheikhbahaei S., Marcus C., Hafezi-Nejad N., Taghipour M., Subramaniam R.M. Value of FDG PET/CT in Patient Management and Outcome of Skeletal and Soft Tissue Sarcomas, niet gevonden omdat in dit artikel in titel, abstract en indexterm niet gesproken wordt over CT thorax.

Vraag is welke strategie voldoet aan de criteria. Als het alleen om CT thorax gaat (onderstaande vragen), dan voldoet vraag 2. Als de nadruk meer ligt op de cancer staging zou vraag 1 meer in aanmerking komen.
Bij vraag 1 loop je het risico dat vergelijkende studies van CT thorax vs. X-ray-thorax worden gemist op het moment dat er niet over staging wordt gesproken. Staging is een voorwaarde om te worden meegenomen. Bij het uitvoeren van vraag 2 worden artikelen gemist zoals het sleutelartikel van Sheikbahaei omdat niet over CT thorax wordt gesproken.

Als op alle vragen antwoord gegeven moet worden zou je nog kunnen kiezen voor een combinatie van beide vragen:

3. Soft tissue sarcome EN CT EN (cancer staging of thorax)

In dit geval worden in 1 database in totaal 315 diagnostische studies gevonden (SR + observationeel)

Te gebruiken voor richtlijnen tekst:
In de databases Embase en Ovid/Medline is op 2-12-2022 met relevante zoektermen gezocht vanaf 2005 naar diagnostische systematische reviews, RCTs en observationele studies over de rol van CT thorax bij wekedelentumoren. De literatuurzoekactie leverde 192 unieke treffers op.

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	13	6	15
RCTs	5	4	8
Observationele studies	125	90	169
Overig			
Totaal			192

Zoekstrategie

Embase

No.	Query	Results
#24	#20 NOT #22	3
#23	#6 AND #20	1
#22	#20 AND #21	1
#21	#11 OR #12 OR #13	143
#20	#16 OR #17 OR #18 OR #19	4
#19	'value of fdg pet/ct in patient management and outcome of skeletal and soft tissue sarcomas'	1
#18	'diagnostic and clinical impact of 18f-fdg pet/ct in staging and restaging soft-tissue sarcomas of the extremities and trunk: mono-institutional retrospective study of a sarcoma referral center'	1
#17	'whole-body magnetic resonance imaging in myxoid liposarcoma: a useful adjunct for the detection of extra-pulmonary metastatic disease'	1
#16	'soft tissue and visceral sarcomas: esmo-euracan-genturis clinical practice guidelines for diagnosis, treatment and follow-up'	1
#15	#13 NOT #12 NOT #11 OBS	125
#14	#12 NOT #11 RCT	5
#13	#6 AND (#9 OR #10)	133
#12	#6 AND #8	5
#11	#6 AND #7 SR	13
#10	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase	13664329

	NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR ('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#9	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#8	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#6	#4 AND #5	3328

#5	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	9511990
#4	#3 AND [1-1-2005]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	10624
#3	#1 AND #2	17435
#2	('computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR (((compute* OR positron) NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw) AND ('thorax'/exp OR chest:ti,ab,kw OR thora*:ti,ab,kw)	193816
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 (sarcoma* OR tumor* OR tumour* OR neoplasm* OR cancer*)):ti,ab,kw)	97965

Ovid/Medline

#	Searches	Results
17	15 not 14 not 13 OBS	90
16	14 not 13 RCT	4
15	8 and (11 or 12)	96
14	8 and 9	5
13	8 and 10 SR	6
12	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind	5301185

	method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
11	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4305250
10	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	633361
9	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1566276
8	6 and 7	238
7	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab.	7618701

	or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	840
5	limit 4 to yr="2005 -Current"	857
4	1 and 2 and 3	1098
3	exp Thorax/ or thora*.ti,ab,kf. or chest*.ti,ab,kf.	435926
2	exp Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf.	818569
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf.	62198

Module 3 – Risico-inschatting

Search and select

Preferably a study measuring the effect of using a prediction model on treatment decisions and the ability of the model to accurately predict overall survival and local recurrence.

As such research is very rare and the working group did not expect to find such studies, a systematic review of the literature was performed to answer the following question: Which model predicts overall survival and local recurrence in patients from patients with soft tissue sarcoma and what is the predictive value of this model?

P	(Patients):	patients with primary extremity soft tissue sarcoma
I	(Intervention):	prediction model ○ outcome: mortality, overall survival, local recurrence ○ factors, at least one of the following: age, grade, sarcoma type, size
C	(Comparison):	other prediction model or no comparison
O	(Outcome):	model performance (discrimination parameters like area under the curve, C-index, sensitivity, specificity, predictive value)
T/S	(Timing/Setting):	pre-operative, during follow-up, with new event

<u>Relevant outcome measures</u>

The guideline development group considered model discrimination as a critical outcome measure for decision making and sensitivity, specificity and predictive values as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

<u>Prognostic research: Study design and hierarchy</u>

When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g. bootstrapping or cross validation) can be used to answer the research question as well, but downgrading the level of evidence is obvious due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models. The risk factors identified from such models can be used to inform patients about the elevated risk on complications during procedural sedation and analgesia, however they are less suitable to be used in clinical decision making.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12-10-2023. The detailed search strategy is depicted under the tab

Methods. The systematic literature search resulted in 1,178 hits. Studies were selected based on the following criteria:

- Prediction model is externally validated
- Prediction model for patients with primary extremity soft tissue sarcoma with outcome overall survival or local recurrence
- Published after 2010

42 studies were initially selected based on title and abstract screening. After reading the full text, 20 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 12 studies were included.

Results

In total, 12 studies that reported 4 different prediction models were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Four externally validated prediction models were identified in the 12 studies that were included in the literature analysis.

MSKCC nomogram

Kattan (2002) developed the MSKCC nomogram. **Eilber (2004)** externally validated the model. **Mariani (2005)** adjusted the grade factor in the nomogram and validated the model for patients with extremity STS. **Squires (2022)** externally validated the revised model from **Mariani (2005)**.

SAM-model

Sampo (2012) developed and externally validated the SAM-model.

Sarculator

Callegaro (2016) developed and externally validated the Sarculator nomogram. The model was also externally validated by **Squires (2022)** and **Voss (2022)**. **Callegaro (2019)** developed and externally validated a dynamic version of the model.

PERSARC

Van Praag (2017) developed the PERSARC nomogram **Smolle (2019)** externally validated the model for the outcome local recurrence. **Rueten-Budde (2018)** developed a dynamic version of the model for the outcome overall survival, which was updated and externally validated by **Rueten-Budde (2021)**.

For more information about the characteristics of the individual studies, see Table 1.

Table 1 – Study characteristics per prediction model

Study	Type of validation	Population	N, survival %	Analysis method
MSKCC nomogram (Memorial Sloan Kettering Cancer Center)				
Kattan, 2002; prospective cohort study	Development, internal validation	Adult patients (> 16 years) with primary STS.	N=2,163, The 5- and 10-year disease-specific death probabilities were 25% and 35%.	Three prediction methods were compared, Kaplan-Meier analysis of all possible subsets,

				recursive partitioning, and Cox proportional hazards regression analysis. Nomogram based on Cox model.
Eilber, 2004; prospective cohort study	External validation	Adult patients (>16 years) with primary soft tissue sarcoma (STS), grade low/ intermediate/ high, tumor completely surgically resected.	N=929, the observed 5-year and 10-year disease-specific survival rates were 77% and 71%.	Only external validation
Mariani, 2005; retrospective cohort study	Revised nomogram, internal validation	Patients with extremity STS, grade 1-3, primary disease, undergoing surgery with curative intent	N=642, 10-year survival estimates 95.8% in patients with Grade 1 STS, 76.5% for Grade 2 STS, and 59.4% for Grade 3 STS.	Multiple Cox regression model.
Squires, 2022; retrospective cohort study	External validation	Patients with primary extremity STS	N=1,326, estimated 5- and 10-year OS of 70% and 58%.	Only external validation
SAM-model				
Sampo, 2012; retrospective cohort, validation on data obtained from hospital register	Development, external validation	Non-metastatic, primary or locally recurrent STS of the extremities or trunk wall	DC N=294, VC N=354. The 5-year sarcoma-specific survival rate was 75% and at 10 years 71%, no data on survival rate in validation cohort.	Multivariate Cox proportional hazards regression.
Sarculator				
Callegaro, 2016; retrospective cohort study	Development, external validation	Patients with extremity STS, after macroscopically complete surgical resection at multidisciplinary sarcoma centres	DC N=1,452; VC1 N=420, VC2 N=1,436, VC3 N=444, 5-year and 10-year overall survival were 79.9% and 72.9% for DC; 78.1% and 68.3% for VC1; 72.7% and 60.2% for VC2; and 72.7% and not estimated (due to the shorter follow-up) for VC3.	Multivariable Cox model, backward procedure based on the Akaike information criterion (AIC) for variable selection.
Callegaro, 2019; retrospective multicenter cohort study	Development dynamic nomogram, external validation	Patients with primary extremity STS	DC N=3,740; VC N=893, DC 5-year and 10-year OS 76.0% and 66.3%; VC 59.5% and 48.0%.	Multivariable Cox model, backward procedure based on the Akaike information criterion (AIC) for variable selection.
Squires, 2022; retrospective cohort study	External validation	Patients with primary extremity STS	N=1,326, estimated 5- and 10-year OS of 70% and 58%.	Only external validation
Voss, 2022; data retrospectively obtained from database	External validation	Patients with soft tissue sarcoma of the extremity or trunk	N=9,738, 5-year OS was 68.9%.	Only external validation
PERSARC (PERsonalized SARcoma Care)				
Van Praag, 2017;	Development, internal validation	Patients with primary high grade extremity STS	N=766, OS was estimated to be equal to 63%, 53% and 39% at 3, 5 and 10	Multivariate Cox proportional hazards regression model (OS),

retrospective cohort study			years, respectively; LR was estimated to be equal to 13.3%, 15.1% and 17.2% at 3, 5 and 10 years, respectively.	Fine and Gray model (LR)
Smolle, 2019; retrospective multicenter cohort study	External validation for outcome LR	Patients with high grade extremity STS	DC N=1931, VC=1085. Two hundred forty-two (12.5%) of test cohort patients developed LR.	Fine and Gray model, stepwise backward selection.
Rueten-Budde, 2018; retrospective multicenter cohort study	Development dynamic model, internal validation outcome dynamic OS	Patients with high-grade extremity STS	N=2,232. No survival rates reported.	Proportional landmark supermodel. Landmark time points tLM were chosen every three months between zero and five years after surgery. At each of these time points a Cox proportional hazards model was estimated on the subset of patients still at risk: patients alive and in follow-up at time tLM. The status of LR and DM is determined at landmark time point tLM for each patient and considered fixed. These Cox models were then combined into a landmark supermodel.
Rueten-Budde, 2021; retrospective cohort study	Revision dynamic model, external validation for dynamic OS	Patients with high-grade extremity STS	Added patients N=3,826; VC N=1,111. No survival rates reported.	The dynamic prediction model developed in Rueten-Budde (2018) was revised by adding more patients and the variable grade to the model. The prediction model was based on landmark methodology.

DC=development cohort, VC=validation cohort, STS=soft-tissue sarcoma, OS=overall survival

Results

Overall survival

MSKCC

The MSKCC nomogram is reported in four studies (**Kattan, 2002; Eilber, 2004; Mariani, 2005; Squires, 2022**). More information about the model characteristics, development and validation is presented in Table 2. Model performance was reported using C-indexes varying from 0.71 to 0.77. The working group considers the performance of this model acceptable.

SAM-model

The SAM-model is reported in the study from **Sampo (2012)**. More information about the model characteristics, development and validation is presented in Table 2. Model performance was reported using AUC values of 0.81 and 0.77 and C-indexes of 0.79 and 0.77. The working group considers the performance of this model acceptable.

Sarculator

The Sarculator nomogram is reported in four studies (**Callegaro, 2016; Callegaro, 2019; Squires, 2022; Voss, 2022**). More information about the model characteristics, development and validation is presented in Table 2. Model performance was reported using C-indexes varying from 0.675 to 0.845. The working group considers the performance of this model acceptable.

PERSARC

The PERSARC nomogram for the outcome overall survival is reported in three studies (**Van Praag, 2017; Rueten-Budde, 2018; Rueten-Budde, 2021**). More information about the model characteristics, development and validation is presented in Table 2. Model performance was reported using C-indexes varying from 0.677 to 0.827. The working group considers the performance of this model acceptable.

Local recurrence

PERSARC – 2 studies

The PERSARC nomogram for the outcome local recurrence is reported in two studies (**Van Praag, 2017; Smolle, 2019**). More information about the model characteristics, development and validation is presented in Table 2. Model performance was reported using C-indexes varying from 0.683 to 0.705. **Smolle (2019)** reported that calibration plots for LR using test and validation cohort showed that the LR model tended to underestimate the actual patient risk, especially in the validation cohort.

Table 2 – Prediction model characteristics and outcomes

Prediction model name	Outcome	Predictors: effect size (95%CI)	Performance measure (95%CI)
MSKCC nomogram (Kattan, 2002; Mariani, 2005)	12-year sarcoma-specific death after surgery *(Mariani 2005: 10-year extremity STS-specific death)*	Age at diagnosis Tumor size (< 5, 5 to 10, or > 10 cm) Histologic grade (high or low), in Mariani 2005 changed to FNCLCC-grade (1-3) Histologic subtype (fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve tumor, synovial, or other) Depth (superficial or deep) Site (upper extremity, lower extremity, visceral, thoracic or trunk, retrointraabdominal, or head or neck) No effect sizes reported.	*Development (Kattan 2002)* C-index: 0.77
			External validation (Eilber 2004) C-index: 0.76
			Internal validation adjusted model (Mariani 2005) C-index 0.76
			External validation of Mariani 2005 (Squires 2022) C-index 0.71 (0.68 to 0.75) for 4-, 8-, and 12-year DSS

SAM model (Sampo, 2012)	10-year sarcoma-specific survival from diagnosis	Tumor size per cm: HR 1.10 (1.05 to 1.15) Necrosis (no/yes): HR 1.60 (0.88 to 2.90) Vascular invasion (no/yes): HR 1.60 (0.93 to 2.75) Histological grade (2/3/4, per grade): HR 1.57 (1.11 to 2.22) Tumor depth (superficial/ deep): HR 3.51 (1.71 to 7.38) Location (extremity/ axis of body): HR 1.65 (1.01 to 2.68)	*Development (Sampo 2012)* AUC 0.81 (0.75 to 0.87) C-index 0.79 *External validation (Sampo 2012)* AUC 0.77 (0.72 to 0.82) C-index 0.77
Sarculator (Callegaro, 2016; Callegaro, 2019)	10-year OS *(Callegaro 2019: dynamic 5-year OS)*	Age (66 vs 40 years, third and first quartile): HR 1.58 (1.30 to 1.93) Tumor size (10 vs 4 cm, third and first quartile): HR 2.48 (1.92 to 3.21) FNCLCC grade: II vs I HR 2.68 (1.64 to 4.39), III vs I HR 4.25 (2.64 to 6.84) Histological subtype Leiomyosarcoma vs myxoid liposarcoma: HR 2.50 (1.51 to 4.16) DD/pleom lipo vs myxoid liposarcoma: HR 1.48 (0.80 to 2.74 MPNST vs myxoid liposarcoma: HR 1.89 (1.06 to 3.36) Myxofibrosarcoma vs myxoid liposarcoma: HR 1.64 (0.99 to 2.70) Synovial vs myxoid liposarcoma: HR 2.70 (1.59 to 4.60) UPS vs myxoid liposarcoma: HR 1.27 (0.76 to 2.11) Vascular vs myxoid liposarcoma: HR 5.81 (2.71 to 12.45) Other vs myxoid liposarcoma: HR 1.99 (1.23 to 3.21)	*Development cohort (Callegaro 2016)* C-index 0.767 (0.743 to 0.789) *External validation cohorts (Callegaro 2016)* C-index 0.698 (0.638 to 0.754) C-index 0.775 (0.754 to 0.796) C-index 0.762 (0.720 to 0.806) *Development cohort dynamic model (Callegaro 2019)* C-index At time of primary surgery: 0.776 (0.761 to 0.790) 1 year after surgery: 0.837 (0.822 to 0.851) 2 years after surgery: 0.845 (0.823 to 0.862) 3 years after surgery: 0.834 (0.811 to 0.859) *External validation dynamic model (Callegaro 2019)* C-index At time of primary surgery: 0.675 (0.643 to 0.704) 1 year after surgery: 0.773 (0.740 to 0.801) 2 years after surgery: 0.810 (0.775 to 0.844) 3 years after surgery: 0.796 (0.751 to 0.834) *External validation (Squires 2022)* C-index 5-year OS: 0.72 (0.70 to 0.75) C-index 10-year OS: 0.73 (0.70 to 0.75) *External validation (Voss 2022)* C-index 5-year OS 0.726
PERSARC (Van Praag, 2017;	Overall survival at 3, 5 and 10 years	Age (unit increase of 10 years): HR 1.195 (1.116 to 1.268)	*Development (Van Praag 2017)* C-index 0.677 (95% CI 0.643 to 0.701)

Rueten-Budde, 2018)	*(Rueten-Budde, 2018/2021: dynamic 5-year OS)*	Size (unit increase of 1 cm): HR 1.068 (1.052 to 1.085) Depth (relative to investing fascia) Superficial vs deep: HR 0.813 (0.591 to 1.117) Deep and superficial vs deep: HR 1.110 (0.736 to 1.674) Histology MPNST vs myxofibrosarcoma: HR 1.422 (0.989 to 2.044) Synovial sarcoma vs myxofibrosarcoma: HR 1.261 (0.869 to 1.831) Spindle cell sarcoma vs myxofibrosarcoma: HR 1.211 (0.884 to 1.661) MFH/UPS vs myxofibrosarcoma: HR 1.293 (0.890 to 1.876) Margin 0.1 to 0.2 mm vs 0 mm: HR 0.786 (0.599 to 1.033) > 2 mm vs 0 mm: HR 0.711 (0.524 to 0.964) RT Neoadjuvant vs no RT: HR 0.548 (0.399 to 0.753) Adjuvant vs no RT: HR 0.638 (0.486 to 0.837)	*Development dynamic model, validation (Rueten-Budde 2018)* C-indexes 0.694, 0.777, 0.813, 0.810, 0.798, and 0.781 at 0-, 1-, 2-, 3-, 4-, and 5-years after surgery respectively *Revision, external validation (Rueten-Budde 2021)* C-indexes 0.697, 0.790, 0.822, 0.818, 0.812, and 0.827 at 0, 1, 2, 3, 4, and 5 years after surgery respectively
	Local recurrence (cumulative incidence)	Age (unit increase of 10 years): sHR 1.051 (0.942 to 1.184) Size (unit increase of 1 cm): sHR 1.031 (1.001 to 1.063) Depth (relative to investing fascia) Superficial vs deep: sHR 0.907 (0.536 to 1.535) Deep and superficial vs deep: sHR 0.563 (0.198 to 1.604) Histology MPNST vs myxofibrosarcoma: sHR 1.079 (0.580 to 2.009) Synovial sarcoma vs myxofibrosarcoma: sHR 0.779 (0.379 to 1.602) Spindle cell sarcoma vs myxofibrosarcoma: sHR 0.979 (0.570 to 1.681) MFH/UPS vs myxofibrosarcoma: sHR 1.096 (0.557 to 2.156) Margin 0.1 to 0.2 mm vs 0 mm: sHR 0.635 (0.406 to 0.992) > 2 mm vs 0 mm: sHR 0.282 (0.159 to 0.500) RT Neoadjuvant vs no RT: sHR 0.312 (0.146 to 0.668)	*Development (Van Praag 2017)* C-index 0.696 (95% CI 0.629 to 0.743) *Smolle 2019* C-index 0.705 and 0.683 for the internal and external cohort respectively

		Adjuvant vs no RT: sHR 0.700 (0.417 to 1.175)	

AUC=area under the ROC (receiver operating characteristic) curve, C-index=concordance index, (s)HR=(sub distribution) hazard ratio, CI=confidence interval, OS=overall survival, DSS=disease-specific survival, LR=local recurrence, STS=soft-tissue sarcoma, FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer, DD/pleom lipo=dedifferentiated/pleomorphic liposarcoma, MPNST=malignant peripheral nerve sheath tumor, UPS=undifferentiated pleomorphic sarcoma, MFH=malignant fibrous histiocytoma, RT=radiotherapy.

Level of evidence of the literature

MSKCC: model including age, tumor size, histologic grade, histologic subtype, dept, site – predicting sarcoma-specific death

The level of evidence regarding the outcome measure started at high and was downgraded by two levels to **LOW** because of study limitations (risk of bias, -1); confidence intervals crossing the border of clinical relevance (imprecision, -1).

SAM-model: model including tumor size, necrosis, vascular invasion, histological grade, depth, location – predicting sarcoma-specific survival

The level of evidence regarding the outcome measure started at high and was downgraded by two levels to **LOW** because of study limitations (risk of bias, -1); applicability because the study also included patients with recurrent and/ or trunk wall STS (indirectness, -1).

Sarculator: model including age, tumor size, grade and histological subtype – predicting (dynamic) overall survival

The level of evidence regarding the outcome measure started at high and was downgraded by one level to **MODERATE** because of confidence intervals crossing the border of clinical relevance (imprecision, -1).

PERSARC: model including age, tumor size, depth, histology, margin, RT – predicting (dynamic) overall survival

The level of evidence regarding the outcome measure started at high and was downgraded by one level to **MODERATE** because of confidence intervals crossing the border of clinical relevance (imprecision, -1).

PERSARC: model including age, tumor size, depth, histology, margin, RT – predicting local recurrence

The level of evidence regarding the outcome measure started at high and was downgraded by one level to **MODERATE** because of confidence intervals crossing the border of clinical relevance (imprecision, -1).

Conclusions

Low GRADE	The MSKCC prediction model (including the factors age, tumor size, histologic grade, histologic subtype, dept, site) may show good performance for predicting sarcoma-specific death in patients with extremity soft-tissue sarcoma after surgical resection. *Source: Kattan, 2002; Eilber, 2004; Mariani, 2005; Squires, 2022*

Low GRADE	The SAM prediction model (including the factors tumor size, necrosis, vascular invasion, histological grade, depth, location) may show good performance for predicting sarcoma-specific survival after surgical resection in patients with extremity soft-tissue sarcoma.

	Source: Sampo, 2012

Moderate GRADE	The Sarculator prediction model (including the factors age, tumor size, grade and histological subtype) likely shows good performance for predicting (dynamic) overall after surgical resection survival in patients with extremity soft-tissue sarcoma. *Source: Callegaro, 2016; Callegaro, 2019; Squires, 2022; Voss, 2022*

Moderate GRADE	The evidence suggests that the PERSARC prediction model (including the factors age, tumor size, depth, histology, margin, RT) likely shows good performance for predicting (dynamic) overall after surgical resection survival in patients with extremity soft-tissue sarcoma. *Source: Van Praag, 2017; Rueten-Budde, 2018; Rueten-Budde; 2019*

Moderate GRADE	The PERSARC prediction model (including the factors age, tumor size, depth, histology, margin, RT) likely shows moderate to good performance for predicting local recurrence. The model may underestimate the risk of local recurrence after surgical resection in patients with extremity soft-tissue sarcoma. *Source: Van Praag, 2017; Smolle, 2019*

Kennislacunes

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Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	geen	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Evidence table for prediction modelling studies (based on CHARMS checklist)

Study reference	Study characteristics	Patient characteristics	Candidate predictors	Model development, performance and evaluation	Outcome measures and results	Comments Interpretation of model
Kattan, 2002 *Development MSKCC model*	Source of data and date: prospective cohort, July 1982 through May 2000 Setting/ number of centres and country: single institution, NY, USA Funding and conflicts of interest: Supported in part by grant no. RPG-00-202-01-CCE (to M.W.K.) from the American Cancer Society and grant no. P0-CA-47179-11 (to M.F.B.) from the National Cancer Institute. COI not reported.	Recruitment method: consecutive Inclusion criteria: Adult patients (> 16 years of age) who underwent treatment for primary soft tissue sarcoma at Memorial Sloan-Kettering Cancer Center. Exclusion criteria: Patients who presented with local or systemic recurrence were excluded from this study. Treatment: All patients were treated with surgical resection. Some patients received adjuvant chemotherapy or radiation at the discretion of the multidisciplinary soft tissue sarcoma group or as part of clinical trials. Because treatment was not prospectively randomized but included	<u>Age:</u> Age at diagnosis <u>Tumor size:</u> ≤5, 5 to 10, or > 10 cm <u>Histologic grade:</u> High or low <u>Histologic subtype:</u> fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve tumor, synovial, or other. <u>Tumor depth:</u> superficial or deep <u>Tumor site:</u> Upper extremity, lower extremity, visceral, thoracic or trunk, retro intraabdominal, or head or neck. Missing data: Patients whose sarcoma site was skin (n=25) were excluded. Patients with	**Development** Modelling method: Three nomogram development approaches were compared: Kaplan-Meier, recursive partitioning, and Cox regression. The Cox regression model was used to develop the nomogram. **Performance** Calibration measures: 'excellent' calibration according to authors, shown in calibration plot. Discrimination measures and 95%CI: C-index: 0.77 Classification measures: Not reported. **Evaluation** Method for testing model performance: internal.	Type of outcome: single Definition and method for measurement of outcome: Disease-specific survival rates, death from sarcoma or treatment complication was considered an event. Endpoint or duration of follow-up: Until death, maximum follow-up 18.1 years Number of events /outcomes: The median follow-up overall and for the patients still alive was 3.2 and 4.0 years; the 5- and 10-year disease-specific death probabilities were 25% (95% CI, 23% to 27%) and 35% (95% CI, 32% to 38%) respectively. **RESULTS** Multivariable model: Age at diagnosis Tumor size (< 5, 5 to 10, or > 10 cm) Histologic grade (high or low), in Mariani 2005 changed to FNCLCC-grade (1-3)	<u>Interpretation</u>: confirmatory. <u>Authors' conclusion</u> In conclusion, the nomogram estimates the probability that the patient will die of sarcoma within 12 years, assuming he or she does not die of another cause first. Such probability estimates may be useful for patient counseling, follow-up scheduling, and clinical trial eligibility determination.

		both patients prospectively randomized in trials and those given standard of care based on prognosis, treatment variables were omitted from modeling. <u>Participants:</u> N= 2,136 Mean age: 50.9 years Sex: % M / % F Not reported.	one or more missing values (n=139) were omitted, leaving 2,163 patients for analysis.		Histologic subtype (fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve tumor, synovial, or other) Depth (superficial or deep) Site (upper extremity, lower extremity, visceral, thoracic or trunk, retro intraabdominal, or head or neck) No effect sizes reported.	
Eilber, 2004 *MSKCC, external validation Kattan 2002*	Source of data and date: prospectively recorded hospital data, between 1975 and 2002. Setting/ number of centres and country: department of surgery, University of California–Los Angeles (UCLA; Los Angeles, CA) Funding and conflicts of interest: "Supported by National Institutes of Health Program Project Grant P01CA47179 (M.F.B.), a Kristen Ann Carr Fellowship (F.C.E.), and	Recruitment method: consecutive Inclusion criteria: patients who underwent treatment for primary STS at UCLA. Exclusion criteria: Patients who presented with locally recurrent or metastatic disease were excluded from the analysis. All patients with STS who were treated with an ifosfamide-based chemotherapy protocol (n = 238 between 1990 and 2002) were excluded, due to evidence that ifosfamide-based chemotherapy is	N/A (external validation only)	**Development** N/A **Performance** Calibration measures and 95%CI: calibration plots reported for nomogram with and without patients with intermediate grade disease. Model is considered to be very well calibrated according to the authors. Discrimination measures and 95%CI: C-index 0.76 Classification measures: NR **Evaluation** Method for testing model performance: separate external validation	Type of outcome: single Definition and method for measurement of outcome: 12-year disease specific survival. Disease-specific survival was defined as the time from surgery to death caused by disease or to last follow-up. Endpoint or duration of follow-up: NR. Number of events/outcomes: With median follow-up periods of 48 months for all patients and 60 months for surviving patients, the observed 5-year and 10-year disease-specific survival rates were 77% (95% CI, 74– 80%) and 71% (95% CI, 67–75%), respectively.	<u>Interpretation</u>: confirmatory. <u>Authors' conclusion</u> In conclusion, the MSKCC Sarcoma Nomogram was found to yield accurate survival predictions when applied to an external cohort consisting of patients who were treated at UCLA.

	American Cancer Society Grant RPG-00-202-01-CCE (M.W.K.)." COI not reported.	associated with improved survival in patients with high-risk primary extremity STS. Treatment: All patients had their primary tumors completely surgically resected at UCLA. A significant number of patients received adjuvant radiation therapy and/or adjuvant chemotherapy. Adjuvant therapy was administered at the discretion of the multidisciplinary sarcoma research group or as part of a clinical trial. Participants: 929 patients Mean age: 49 years Sex: % M / % F NR Other important characteristics: Tumor grade Low: 272 (29%) Intermediate: 200 (21%) High: 457 (50%)			**RESULTS** Multivariable model: MSKCC model from Kattan 2002 used.	
Mariani, 2005 *MSKCC adaptation*	Source of data and date: Data from institute, between January	Recruitment method: consecutive Inclusion criteria:	Predictors same as MSKCC model Kattan 2002, only histologic	**Development** Modelling method: For MSKCC model testing and revision, we adopted the	Type of outcome: single Definition and method for measurement of outcome:	Interpretation: confirmatory Authors' conclusion

model Kattan 2002	1980 and December 2000 Setting/ number of centres and country: the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) (Milan, Italy). Funding and conflicts of interest: NR	patients with localized extremity STS underwent surgery with curative intent, who presented with primary disease Exclusion criteria: - Treatment: All surgical resections were macroscopically complete, which we defined as the absence of macroscopic residual disease after surgical excision of the tumor. Adjuvant radiation therapy was delivered to 237 patients (37%). External beam radiation was used in all such patients, and the doses ranged from 45 grays (Gy) to 65 Gy (median, 57 Gy). Adjuvant chemotherapy (mainly anthracycline-based regimens associated with ifosfamide) was given to 114 patients (18%) at the discretion of the multidisciplinary STS group or as part of clinical trials. <u>Participants:</u> 642 patients Mean age: 47.7 years	grade 1-3 instead of high vs low. Missing data: NR	approach of "validation by calibration", Cox model. **Performance** Calibration measures and 95%CI: "Graphic comparison of observed and predicted sarcoma-specific survival curves showed that predictions by the nomogram were quite accurate, within 10% of actual survival for all prognostic strata. Statistical analysis showed that such predictions could be improved by employing approximately 25% shrinkage to achieve good calibration" Discrimination measures and 95%CI: C-statistic: 0.76 Classification measures: NR **Evaluation** Method for testing model performance: "To account for possible over fitting, we calculated the degree of shrinkage of Cox model regression coefficients and the optimism in the estimated c statistic by means of bootstrap"	10-year extremity STS-specific death: "Survival time, which was computed from the date of surgery to the date of death or last follow-up, was censored for living patients and for patients who died of causes unrelated to STS, because we modeled disease-specific death." Endpoint or duration of follow-up: 120 months Number of events/outcomes: There were 176 deaths overall; of these, 143 deaths (81%) were due to sarcoma and, thus, contributed to the current analysis. **RESULTS** Multivariable model: Only HR reported for adjusted predictor. Histologic grade Grade 2 vs. Grade 1 HR 4.51 (95% CI 1.99 to 10.2) Grade 3 vs. Grade 1 HR 8.93 (95%CI 4.14 to 19.3)	In conclusion, the current study confirmed that the MSKCC nomogram is a valuable tool for individual prognostic assessment. However, some degree of adjustment seems useful for improving the quality of predictions. This hypothetically may reflect either statistical "over fitting" in the original model, weaker prognostic effect of covariates in extremity STS compared with STS in other sites, the application of a three-grade system instead of two-grade system, or some combination of the above mechanisms. The revised nomogram incorporates such an adjustment of predictions, and it is proposed as an extension in extremity STS of the MSKCC nomogram whenever histologic grade is classified according to the FNCLCC system, which is now the system used most widely all over the world.

		Sex: % M / % F 52/48 Other important characteristics: Histologic grade: Grade 1: 180 (28%) Grade 2: 170 (26%) Grade 3: 292 (46%)				
Squires 2022 *External validation MSKCC (Mariani 2005) / Sarculator (Callegaro 2016)*	Source of data and date: U.S. Sarcoma Collaborative (USSC) database, from 2000 to 2017 Setting/ number of centres and country: nine high-volume academic institutions across the United States Funding and conflicts of interest: FUNDING This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. DISCLOSURES The authors have no financial or conflict of interest disclosures.	Recruitment method: consecutive Inclusion criteria: all patients who underwent resection of primary extremity STS. Patients aged 18 years or older who underwent curative intent resection of primary extremity STS were included. Exclusion criteria: Histologies excluded from the original Sarculator nomogram development study were also excluded in the current analysis: desmoid fibromatosis, peripheral primitive neuroectodermal tumor (PPNET), alveolar or embryonal rhabdomyosarcoma, dermatofibrosarcoma protuberans, and well-differentiated liposarcoma.	N/A (external validation only)	**Development** N/A **Performance** Calibration measures: Calibration plots: The calibration plots showed good predictability according to the authors for 5- and 10-year OS using the Sarculator nomogram. The calibration plots for DSS demonstrated similarly good calibration using the MSKCC nomogram. Discrimination measures and 95%CI: Sarculator: The C-indices for 5- and 10-year OS were 0.72 (95% CI: 0.70–0.75) and 0.73 (95% CI: 0.70–0.75). MSKCC: C-indices for 4-, 8-, and 12-year of 0.71 (95% CI: 0.68–0.75) Classification measures: NR **Evaluation** Method for testing model performance:	Type of outcome: single Definition and method for measurement of outcome: Sarculator: overall survival MSKCC: disease-specific survival Endpoint or duration of follow-up: NR Number of events/outcomes: Median follow-up time was 34 months. Median OS was 173 months (IQR, 128 months-MNR), with estimated 5- and 10-year OS of 70% and 58%, respectively. **RESULTS** Multivariable model: N/A (external validation) Alternative presentation of final model: N/A (external validation)	<u>Interpretation</u>: confirmatory. <u>Authors' conclusion:</u> In conclusion, the Sarculator and MSKCC nomograms were both found to have good discriminative and prognostic ability within a diverse, modern, multi-institutional U.S. validation cohort of patients undergoing resection of primary extremity STS. Ongoing incorporation of these prognostic nomograms into the clinical management of extremity STS patients appears warranted.

		Patients with metastatic or recurrent disease were excluded. Treatment: All patients underwent curative intent resection of primary extremity STS. Perioperative Chemotherapy (n=313 (24%)) and radiation (n=700 (53%)) data also were collected. Participants: N=1,326 Median age [IQR]: 59 [46–71] Sex: % M / % F 54/46				
Sampo, 2012 *Development and external validation SAM-model*	Source of data and date: Patients referred during 1987–2002 Swedish database: 25-year period 1973–1997 Setting/ number of centres and country: Helsinki University Central Hospital, Finland, external validation from Lund	Recruitment method: consecutive Inclusion criteria: All patients referred for non-metastatic, primary or locally recurrent STS of the extremities or trunk wall to the Soft Tissue Sarcoma Group between August 1987 and December 2002 are included. Exclusion criteria:	<u>Necrosis:</u> Absent or present. <u>Vascular invasion:</u> Absent or present. <u>Tumor size:</u> In cm, recorded as the largest diameter of tumor in the surgical specimen reported by the original pathologist. <u>Histological grade:</u> The pathologist assigned the histological	**Development** Modelling method: Cox regression multivariate model **Performance** Calibration measures and 95%CI: Calibration plots reported: "A good concordance is seen in the groups with a predicted 10-year survival of over 50%, whereas a slight underestimation is observed in the groups predicted to have the lowest survival." Discrimination measures and 95%CI: AUC: 0.81 (95% CI 0.75–0.87)	Type of outcome: single Definition and method for measurement of outcome: Sarcoma-specific survival (SSS) was calculated from the date of the diagnosis to death from sarcoma. Deaths due to other causes than sarcoma were censored. Endpoint or duration of follow-up: Until death. Number of events/outcomes:	<u>Interpretation</u>: exploratory <u>Authors' conclusion</u> In conclusion, we have created a new prognostic model to estimate survival probability in patients with the commonest subtypes of STS. An external validation was performed showing a good prognostic accuracy and an improvement in accuracy compared with a model with size, necrosis, and vascular invasion only. Our

	University Hospital register, Sweden Funding and conflicts of interest: The study was supported by the Helsinki University Central Hospital Research Funds, Finnish Cancer Society, and the Sigrid Juselius Foundation. Dr M Sampo was supported by grants from the K Albin Johansson Foundation, Finska Läkaresällskapet, and Duodecim Foundation. COI not reported.	Exclusion criteria comprised: extra skeletal osteosarcoma, chondrosarcoma, Ewing/ PNET family tumour, angiosarcoma, alveolar soft tissue sarcoma, epithelioid sarcoma, clear cell sarcoma, atypical lipoma/grade I liposarcoma, dermatofibrosarcoma protuberans or preoperative radiation therapy. A total of 15 patients with chemotherapy were also excluded. Treatment: The primary treatment in all cases was a surgical resection. If the preoperative investigations indicated that adequate surgical margins were not achievable, surgery aimed at marginal surgical margins with postoperative radiation therapy. The treatment protocol recommended, following intralesional surgery, a reoperation when feasible. <u>Participants:</u> N=294 Validation database, N=354	malignancy grade of the tumor based on a four-tiered grading scale modified from Broders et al (1939) and Angervall et al (1986). Grades 1 and 2 are low grades and 3 and 4 high grades. <u>Tumor depth:</u> Subcutaneous tumors with or without cutaneous extension but without involvement of the deep fascia were defined superficial, all others deep. <u>Tumor location:</u> Extremity or axis of body Missing data: In 84 cases, we were unable to retrieve the original histological slides leaving 294 tumours to analysis. Demographic data for missing cases was similar except for histological subtype.	C-index: 0.79 Validation series: AUC: 0.77 (95% CI 0.72–0.82) C-index: 0.77 Classification measures: Compared to SIN model: when the patients were classified into three categories (cutoff at tertiles) on the basis of their predicted 10-year sarcoma-specific survival, the net reclassification improvement (NRI 0.12, P=0.03) is significant as well as the integrated discrimination improvement (IDI 0.03, P=0.0003 **Evaluation** Method for testing model performance: external	The median follow-up for the patients alive at the end of follow-up was 7.2 years (range 0.3–17.5 years). The 5-year sarcoma-specific survival rate was 75% (95% CI 0.70–0.80) and at 10 years 71% (95% CI 0.64–0.76) **RESULTS** Multivariable model: Tumor size per cm: HR 1.10 (1.05 to 1.15) Necrosis (no/yes): HR 1.60 (0.88 to 2.90) Vascular invasion (no/yes): HR 1.60 (0.93 to 2.75) Histological grade (2/3/4, per grade): HR 1.57 (1.11 to 2.22) Tumor depth (superficial/ deep): HR 3.51 (1.71 to 7.38) Location (extremity/ axis of body): HR 1.65 (1.01 to 2.68)	model can be seen as a working formulation to be refined by validation in further external validation studies and is made available online.

		Mean age (range) 57 (16-92) Validation database 63 (17-96) Sex: % M / % F 52/48 Validation database: 56/44				
Callegaro, 2016 *Development and external validation Sarculator model*	Source of data and date: Development cohort: 1 Jan 1994, to 31 Dec 2013 External validation, cohort 1: 1 Jan 1996 to 15 May 2012, cohort 2: 1 Jan 1994 to 31 Dec 2013, cohort 3: 1 Jan 2006 to 31 Dec 2013 Setting/ number of centres and country: Development cohort: Istituto Nazionale Tumori (Milan, Italy). Validation cohorts: Institut Gustave Roussy (Villejuif, France), Mount Sinai Hospital (Toronto, ON, Canada), Royal Marsden Hospital (London, UK) Funding and conflicts of interest:	Recruitment method: Consecutive Inclusion criteria: All consecutive adult (aged >18 years) patients with primary (non-recurrent and non-metastatic) soft-tissue sarcomas of the extremities, who had had an operation with curative intent at Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy), between Jan 1, 1994, and Dec 31, 2013, formed the development cohort of the study. We defined soft-tissue sarcomas of the extremities as all tumours arising from the shoulder girdle to the hand (upper extremity) and from the pelvic girdle (excluding endopelvic tumours) to the foot (lower extremity). Exclusion criteria:	<u>Age at diagnosis:</u> In years. <u>Tumor size:</u> In cm. <u>Tumor depth:</u> Superficial or deep according to the investing fascia. <u>Surgical margins:</u> We classified all macroscopically complete resections according to the closest surgical margin, which we microscopically categorised as either positive (tumour within 1 mm from the inked surface; R1) or negative (absence of tumour within 1 mm from the inked surface; R0). We excluded macroscopically incomplete resection from the analysis. <u>Tumor grading:</u> Fédération Française des Centres de Lutte Contre le Cancer (FNCLCC;	**Development** Modelling method: Multivariable Cox model, backward selection. **Performance** Calibration measures and 95%CI: Well-calibrated according to authors. Calibration plot, Hosmer–Lemeshow calibration test reported. Discrimination measures, C-index (95% CI): DC: 0.767 (0.743 to 0.789). VC1: 0.698 (0.638 to 0.754) VC2: 0.775 (0.754 to 0.796) VC3: 0.762 (0.720 to 0.806) Classification measures: Not reported. **Evaluation** Method for testing model performance: internal and external	Type of outcome: single Definition and method for measurement of outcome: Overall survival (events: deaths from any cause) Endpoint or duration of follow-up: The median follow-up was 86 months (IQR 47–123) for the development cohort; 75 months (46–117) for the French validation cohort, 85 months (44–121) for the Canadian validation cohort, and 54 months (30–71) for the UK validation cohort Number of events/outcomes: In the development cohort, overall survival was 79.9% (95% CI 77.7–82.1) at 5 years and 72.9% (70.2–75.7) at 10 years follow-up. In the validation cohorts, 5-year and 10-year overall survival were 78.1% (95% CI 73.9–82.6) and 68.3% (62.6–74.5) for French patients; 72.7% (70.2–75.2) and 60.2% (57.0–63.5) for Canadian patients; and 72.7% (68.1–77.5) and not estimated	<u>Interpretation:</u> confirmatory <u>Authors' conclusion</u> Our nomograms are reliable prognostic methods that can be used to predict overall survival and distant metastases in patients after surgical resection of soft-tissue sarcoma of the extremities. These nomograms can be offered to clinicians to improve their abilities to assess patient prognosis, strengthen the prognosis-based decision making, enhance patient stratification, and inform patients in the clinic. It is important to note that these nomograms only apply to adult patients with primary soft-tissue sarcomas of the extremities, who underwent macroscopically complete surgical resection at multidisciplinary sarcoma centres.

	The authors declare no competing interests. Funding: None	We excluded patients with desmoids, soft-tissue Ewing's sarcoma, alveolar or embryonal rhabdomyosarcoma, dermatofibrosarcoma protuberans, and well differentiated liposarcoma because of the peculiar natural histories and treatment strategies for these cancers. Treatment: The indication to administer radiotherapy was given by both the operating surgeon and the radiation oncologist when a higher risk of relapse was thought to exist based on clinical grounds. However, no prospectively selected criteria were used to this end. Chemotherapy was given at the discretion of the multidisciplinary institutional sarcoma board or as part of ongoing clinical trials. <u>Participants:</u> N Development cohort (DC): 1,452 N Validation cohort (VC)1: 420 N VC2: 1,436 N VC3: 444 Median age (IQR):	French Federation of Centers for the Fight against Cancer) Criteria, grades I, II, and III. <u>Histological subtypes:</u> Based on WHO's criteria and grouped into nine categories: leiomyosarcoma, dedifferentiated or pleomorphic liposarcoma, myxoid liposarcoma, malignant peripheral nerve sheath tumours, myxofibrosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, vascular sarcoma (including both epithelioid haemangio-endothelioma [mostly grade 1 and occasionally grade 2] and angiosarcoma [only grade 3]), and others. Number of participants with any missing value? Not reported. How were missing data handled? Not reported.		(due to the shorter follow-up) for the UK patients. **RESULTS** Multivariable model, HR (95% CI): *Age* 66 years vs 40 years: 1.58 (1.30–1.93) *Tumour size* 10 cm vs 4 cm: 2.48 (1.92–3.21) *FNCLCC grade* II vs I 2.68 (1.64–4.39) III vs I 4.25 (2.64–6.84) *Histological subtype* Leiomyosarcoma vs myxoid Liposarcoma: 2.50 (1.51–4.16) DD/pleom lipo vs myxoid liposarcoma: 1.48 (0.80–2.74) MPNST vs myxoid liposarcoma: 1.89 (1.06–3.36) Myxofibrosarcoma vs myxoid Liposarcoma: 1.64 (0.99–2.70) Synovial vs myxoid liposarcoma: 2.70 (1.59–4.60) UPS vs myxoid liposarcoma: 1.27 (0.76–2.11) Vascular vs myxoid liposarcoma: 5.81 (2.71–12.45) Other vs myxoid liposarcoma: 1.99 (1.23–3.21) Alternative presentation of final model: Nomogram, free app called Sarculator has been developed	

		DC: 54 (40-66) VC1: 51 (38-62) VC2: 57 (43-70) VC3: 63 (50-74) Sex: % M / % F DC: 54/46 VC1: 51/49 VC2: 56/44 VC3: 57/43			for smartphones and tablets and is distributed via the official app stores	
Callegaro 2019 *Development and external validation of dynamic Sarculator model*	Source of data and date, setting/ number of centres and country: All consecutive adult (>18years) patients with primary (non-recurrent, non-metastatic) eSTS surgically treated at Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy), Institut Gustave Roussy (Villejuif, France), Mount Sinai Hospital (Toronto, Canada), and at the Royal Marsden Hospital (London ,UK) from 1994 to 2013 were merged, forming the development cohort. On the Milan series, we developed two static nomograms for OS and DM in 2016. Patients with the same	Recruitment method: consecutive Inclusion criteria: Adult (>18years) patients with primary (non-recurrent, non-metastatic) eSTS surgically treated. Extremity STS were defined as tumors arising between the shoulder girdle and the hand (upper extremity) and between the pelvic girdle (excluding endopelvic tumours) and the foot (lower extremity). Exclusion criteria: Patients with well-differentiated liposarcoma, dermatofibrosarcoma protuberans, desmoid-type fibromatosis, Ewing sarcoma and alveolar or embryonal rhabdomyosarcoma were excluded.	Predictors (candidate & selected): In the multivariable Cox landmark OS supermodel, after application of the backward procedure the following variables were excluded from the covariates set: tumor's depth, surgical margin status, CTx administration, RTx administration. The final supermodel included age at surgery, tumor size and its interaction with T_{LM}, grading and its interaction with T_{LM}, histology, and both LR and DM indicator variables.	**Development** Modelling method: The dynamic nomogram was developed using a landmark analysis approach and a multivariable Cox model. A backward procedure based on the Akaike Information Criterion was adopted for variable selection. **Performance** Calibration measures: Calibration plots were reported, good calibration according to authors. Discrimination measures and 95%CI: In the development series, the Harrell C index was (95% bootstrap confidence interval) 0.776 (0.761–0.790) for predictions calculated at time of primary surgery (T_{LM}=0) and 0.837 (0.822–0.851), 0.845 (0.823–0.862) and 0.834 (0.811–0.859) for predictions calculated at 1 year, 2 years and 3 years after surgery, respectively. In the validation series, the Harrell C index was 0.675 (0.643–0.704) at T_{LM}=0, 0.773 (0.740–0.801) at T_{LM}=12 months, 0.810 (0.775–0.844) at T_{LM}=24 months and 0.796 (0.751–0.834) at T_{LM}=36 months.	Type of outcome: single Definition and method for measurement of outcome: 5-year overall survival at different times during the first three years of follow-up. Endpoint or duration of follow-up: NR Number of events/outcomes: The median follow-up was (interquartile [IQ] range) 79 months (44–119 months) for the development cohort and 71 months (43–108 months) for the validation cohort. In the development and validation cohorts, respectively, 1003 and 367 patients died. In the development cohort, 5-year OS was 76.0% (74.6–77.5%) and 10-year OS was 66.3% (64.3–68.2%). In the validation cohort 5- and 10-year OS was 59.5% (56.0–63.1%) and 48.0% (43.8–52.6%), respectively. **RESULTS**	<u>Interpretation</u>: confirmatory <u>Authors' conclusion</u> In conclusion, this new prognostic tool fulfills a need of the oncologist dealing with eSTS patients: being able to objectively counsel patients regarding their personalized residual risk during FU. Patients might be comforted from an improvement in prognosis as the time goes by without events and the update of the prognostic estimate may also support patients' planning for the future. Moreover, the dynamic prediction informs the physician of how a postoperative event will impact on an individual patient's prognosis quantitatively. Finally, this study paves the way for future FU personalization with possible creation of risk-adapted FU strategies.

	characteristics operated on between 2000 and 2016 at 7 other European referral centers comprised the validation cohort Funding and conflicts of interest:	Patients who underwent macroscopically incomplete (R2) resections were excluded. Treatment: Patients were operated with curative intent. Radiotherapy (RTx) and/or chemotherapy (CTx) were used according to multidisciplinary guidance or as part of clinical trials. Participants: N development cohort (DC): 3,740 N validation cohort (VC): 893 Median age (IQR): DC: 56 (42–69) VC: 62 (49–73) Sex: % M / % F DC: 54.8/45.2 VC: 55.3/44.7		Classification measures: NR **Evaluation** Method for testing model performance: Internal and external	Multivariable model: Covariates: HR (95% CI) Age, years 69 vs. 42: 1.80 (1.58,2.05) Local recurrence yes vs. no: 5.63 (4.26,7.44) Distant Metastasis yes vs. no: 10.34 (8.74,12.23) Histological subtype LMS vs. Myxoid lipo: 1.78(1.26,2.52) DD/pleom lipo vs. Myxoid lipo: 1.37 (0.93,2.02) MPNST vs. Myxoid lipo: 1.73 (1.16,2.58) Myxofibro vs. Myxoid lipo: 1.05 (0.72,1.53) Synovial sarcoma vs. Myxoid lipo: 2.03 (1.43,2.88) UPS vs. Myxoid lipo:1.18 (0.85,1.63) Vascular vs. Myxoid lipo: 3.20 (1.85,5.53) Other vs. Myxoid lipo: 1.48 (1.07,2.04) Size, cm 11 vs. 4 (0): 3.06 (2.53,3.70) 11 vs. 4 (12): 2.32 (1.92, 2.80) 11 vs. 4 (24): 1.90 (1.55, 2.32) 11 vs. 4 (36): 1.65 (1.29, 2.11) FNCLCC grade II vs. I (0): 2.55 (1.75, 3.73)	

					II vs. I (12): 2.07 (1.42, 3.01) II vs. I (24): 1.63 (1.11, 2.40) II vs. I (36): 1.26 (0.82, 1.94) III vs. I (0): 4.88 (3.40,7.02) III vs. I (12): 2.59 (1.79,3.75) III vs. I (24): 1.59 (1.08, 2.33) III vs. I (36): 1.09 (0.72,1.67) Alternative presentation of final model: dynamic nomogram. The new nomogram has also been incorporated in the app 'Sarculator' for smartphones and tablets, which is available for free download.	
Voss 2022 *External validation Sarculator*	Source of data and date: the National Cancer Data Base (NCDB) Sarcoma Participant Use File (PUF) between 2004 and 2017. Setting/ number of centres and country: The NCDB is a prospectively maintained, national, hospital-based registry that includes data from patients accounting for more than 70% of incident cancer diagnoses at over 1500 Commission on Cancer (CoC)-accredited centers in the USA.	Recruitment method: consecutive Inclusion criteria: Patients with soft tissue sarcoma of the extremity or trunk from the National Cancer Data Base (NCDB) Sarcoma Participant Use File (PUF) between 2004 and 2017 were included. Briefly, we included extremity and trunk sites (ICD-O-3 topography codes C471, C472, C476, C491, C492, and C496) with stage I–III disease by AJCC 8th edition staging. The following histologies were included on the basis of	N/A (external validation only)	**Development** Modelling method: N/A **Performance** Calibration measures: Calibration plots: Sarculator tends to slightly overestimate survival for the higher survival quintiles and tends to underestimate the survival for the subgroup with the lowest actual OS Discrimination measures and 95%CI: C-index of 0.726 Classification measures: NR **Evaluation** Method for testing model performance: External validation	Type of outcome: single Definition and method for measurement of outcome: Overall survival Endpoint or duration of follow-up: NR/until death Number of events/outcomes: mean follow-up time of 4.45 years. The 5-year actual OS for the study cohort was 68.9%. **RESULTS** Multivariable model: N/A (external validation only) Alternative presentation of final model: N/A (external validation only)	Interpretation: confirmatory. Authors' conclusion Sarculator is overall a good predictor of aOS and useful tool for clinicians to aid in survival prognostication, but clinicians should be aware of subpopulations for whom Sarculator's predictions may be stronger or more limited. Future work may focus on enhancing the Sarculator algorithm specifically for US patients, including the incorporation of predictive demographic variables.

	Funding and conflicts of interest: DISCLOSURES None.	their inclusion in the original Sarculator algorithm (ICD-O histology codes in parentheses): leiomyosarcoma (8890, 8891, 8896), liposarcoma [8850, 8855, 8857 (grades 2 and 3 only)], dedifferentiated liposarcoma [8858 (grades 2 and 3 only)], pleomorphic liposarcoma (8854), myxoid liposarcoma (8852–53), malignant peripheral nerve sheath tumor (8540, 8561), myxofibrosarcoma (8840), synovial sarcoma (9040–43), vascular sarcomas (angiosarcoma 8894, 9120; hemangioendothelioma 9130, 9133), undifferentiated pleomorphic sarcoma (8805, 8830), or other sarcoma (8000–01, 8004, 8800–01, 8804, 8810–11, 8813, 8815, 8825, 8895, 9044, 9150, 9170, 9364, 9580, 9581). We included only patients who underwent surgery and had either an R0 (no residual tumor at the primary site) or R1 (microscopic residual tumor) resection as				

		Sarculator was only designed for those who have undergone complete surgical resection. Exclusion criteria: We excluded those with incomplete grade, treatment, or survival data; those with metastatic disease; and those with a tumor <1 cm or > 35 cm in size (maximal size accepted by Sarculator is 35 cm). Treatment: All patients underwent complete surgical resection. Radiation therapy: Neoadjuvant: n=1,941 (19.93%) Adjuvant: 3,856 (39.60%) None: 3,941 (40.47%) Chemotherapy Neoadjuvant or adjuvant: 1,572 (16.14%) Participants: N= 9,738 Age: N(%) • <50: 2,827 (29.03) • 50–59: 1,916 (19.68) • 60–69: 1,999 (20.53) • 70–79: 1,720 (17.66) • ≥ 80: 1,276 (13.10)			

		Sex: % M / % F 54.10/45.90				
Van Praag, 2017 *Development and internal validation PERSARC model*	Source of data and date: retrospective cohort, January 2001 – December 2014 Setting/ number of centers and country: multicenter study, five international sarcoma centers Conflict of interest statement: None declared. Funding: This study was supported by the Dutch Cancer Society - KWF Kankerbestrijding. Role of the funding source: This funding source had no role in the design of this study as well as any role during its execution, analyses, interpretation of the data, in the writing of the report or decision to submit the article for publication.	Recruitment method: consecutive series of patients who underwent surgery Inclusion criteria: Eligible diagnoses included high grade (FNCLCC grade III) angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma and (pleomorphic) soft-tissue sarcomas not-otherwise-specified. Exclusion criteria: Excluded patients include those that were treated without curative intent, had LR or DM within 2 months after primary treatment (ruled out by pre-treatment and follow-up (FU) staging with lung computed tomography (CT) scan), had a tumor in their abdomen, thorax, head or neck or received (neo) adjuvant treatment other than RT or chemotherapy. Treatment received? <u>Participants:</u>	<u>Age:</u> Patient age at presentation. <u>Tumor size:</u> In cm. Maximum diameter at pathologic analysis. In patients that received neoadjuvant RT and/or chemotherapy, tumor size was defined as maximum diameter measured by CT or MRI before treatment. <u>Depth:</u> Relative to the investing fascia: deep, superficial, deep and superficial. <u>Histology subtype:</u> Obtained from medical records: • Myxofibrosarcoma • MPNST • Synovial sarcoma • Spindle cell sarcoma • MFH/UPS • other <u>Surgical margin:</u> • Intralesional: for tumor cells present at the margin of the resection specimen (<0.1 mm) • Marginal: tumor cells found within 0.1 - 2 mm of the margin a	**Development** Modelling method: Outcome OS: multivariate Cox proportional hazards regression model Outcome CILR: Fine and Gray model **Performance** Calibration measures and 95%CI: Calibration plots are reported. Discrimination measures and 95%CI: C-index for OS: 0.677 (95% CI 0.643 to 0.701. C-index for LR: 0.696 (95% CI 0.629 to 0.743) Classification measures: NR **Evaluation** Method for testing model performance: predictive performance of the prediction models was assessed internally by using leave-one-out cross validation (CV).	Type of outcome: Overall survival (OS), cumulative incidence of local recurrence (CILR) Definition and method for measurement of outcome: OS: overall survival at 3, 5 and 10 years after surgery CILR: cumulative incidence of local recurrence in the presence of competing events. LR at 3, 5 and 10 years after surgery Endpoint or duration of follow-up: Patients visited the outpatient clinic for their scheduled clinical and radiographic FU: every 3-4 months in the first 2-3 years, then every 6 months and after 5 years yearly. It was common that FU was ended after 10 years evidence of no disease. Number of events/outcomes: OS was estimated to be equal to 63%, 53% and 39% at 3, 5 and 10 years, respectively; LR was estimated to be equal to 13.3%, 15.1% and 17.2% at 3, 5 and 10 years, respectively. **RESULTS** Multivariable model OS: Age (unit increase of 10 years): HR 1.195 (1.116 to 1.268)	<u>Interpretation</u>: exploratory <u>Authors' conclusion</u> In this study, we developed the PERSARC model which uniquely presents clinicians with the possibility to accurately predict outcome of OS and CILR and compare different treatment modalities, for patients with high-grade ESTS that undergo surgical resection with curative intent.

		N= 766 Mean age ± SD: 58.28 ± 19.39 Sex: % M / % F 57 / 43 Other important characteristics:	• Free: tumor cells found at least 2 mm away from the margin <u>RT:</u> Information from medical records: No RT, neoadjuvant, adjuvant Number of participants with any missing value? N (%): 72 patients (8.6%) of original 838 How were missing data handled? Patients with missing values were not included in the development of the model.		Size (unit increase of 1 cm): HR 1.068 (1.052 to 1.085) Depth (relative to investing fascia) Superficial vs deep: HR 0.813 (0.591 to 1.117) Deep and superficial vs deep: HR 1.110 (0.736 to 1.674) Histology MPNST vs myxofibrosarcoma: HR 1.422 (0.989 to 2.044) Synovial sarcoma vs myxofibrosarcoma: HR 1.261 (0.869 to 1.831) Spindle cell sarcoma vs myxofibrosarcoma: HR 1.211 (0.884 to 1.661) MFH/UPS vs myxofibrosarcoma: HR 1.293 (0.890 to 1.876) Margin 0.1 to 0.2 mm vs 0 mm: HR 0.786 (0.599 to 1.033) > 2 mm vs 0 mm: HR 0.711 (0.524 to 0.964) RT Neoadjuvant vs no RT: HR 0.548 (0.399 to 0.753) Adjuvant vs no RT: HR 0.638 (0.486 to 0.837) Multivariable model LR:	

					Age (unit increase of 10 years): sHR 1.051 (0.942 to 1.184) Size (unit increase of 1 cm): sHR 1.031 (1.001 to 1.063) Depth (relative to investing fascia) Superficial vs deep: sHR 0.907 (0.536 to 1.535) Deep and superficial vs deep: sHR 0.563 (0.198 to 1.604) Histology MPNST vs myxofibrosarcoma: sHR 1.079 (0.580 to 2.009) Synovial sarcoma vs myxofibrosarcoma: sHR 0.779 (0.379 to 1.602) Spindle cell sarcoma vs myxofibrosarcoma: sHR 0.979 (0.570 to 1.681) MFH/UPS vs myxofibrosarcoma: sHR 1.096 (0.557 to 2.156) Margin 0.1 to 0.2 mm vs 0 mm: sHR 0.635 (0.406 to 0.992) > 2 mm vs 0 mm: sHR 0.282 (0.159 to 0.500) RT Neoadjuvant vs no RT: sHR 0.312 (0.146 to 0.668)	

					Adjuvant vs no RT: sHR 0.700 (0.417 to 1.175)	
Smolle, 2019 *Development and validation of dynamic PERSARC model for local recurrence*	Source of data and date: prospectively maintained STS databases at 5 participating tertiary sarcoma referral centers (2 for validation cohort), between January 1994 and October 2014 for the test cohort and between January 2000 and December 2013 for the validation cohort. Setting/ number of centres and country: multicenter study, country NR Funding and conflicts of interest: **Funding:** This work was supported by the Dutch Cancer Society (DCS)—KWF Kankerbestrijding [UL2015-8028]. The funding source had no role in the design of this study; execution, analyses, and interpretation of the data; report writing; or decision to submit the article for publication.	Recruitment method: consecutive Inclusion criteria: Patients with primary nonmetastatic high-grade (G2/3) eSTS managed with surgery at a curative intent were included in the test cohort, with patient information deriving from prospectively maintained STS databases at 5 participating tertiary sarcoma referral centers. Extremity STS were defined as tumors from the shoulder to the fingers (=upper limb) and from the pelvic girdle, excluding intrapelvic STS, to the foot (=lower limb). Exclusion criteria: Patients with missing information on oncological follow-up (i.e., development of LR/DM) had to be excluded (n = 42). Treatment: All patients underwent surgery at a curative intent. (Neo-)adjuvant RTX and CTX had been	Gender, tumor size, histological subtype (except for angiosarcoma/vascular sarcoma (p = 0.127) and dedifferentiated/ pleomorphic liposarcoma (p = 0.254), margins, neoadjuvant and adjuvant RTX, as well as adjuvant CTX (all p < 0.05) had a significant influence on risk of LR in the stepwise backward selection of the Fine and Gray model. Grading as a time-dependent effect was kept in the model (p = 0.108), while age (p = 0.082) and neoadjuvant CTX (p = 0.214) were excluded. Consequently, gender, grading, tumor size, neoadjuvant and adjuvant RTX, histological subtype, and adjuvant CTX were included in the flexible parametric competing risk regression model	**Development** Modelling method: Royston and Parmar approach to fit a flexible parametric competing risk regression model in order to estimate the risk of LR and DM, with death as the competing event; variable selection for the LR and DM models was based on a stepwise backward procedure using a multivariable Fine and Gray model **Performance** Calibration measures and 95%CI: The authors concluded that calibration plots for LR using test and validation cohort showed that the LR model tended to underestimate the actual patient risk, especially in the validation cohort. Discrimination measures and 95%CI: The Harrell C index for LR was equal to 0.705 and 0.683 for the internal and external cohort, respectively. Classification measures: NR **Evaluation** Method for testing model performance: Internal and external	Type of outcome: single. (second model with outcome DM not included in present analysis) Definition and method for measurement of outcome: Local recurrence, defined as a radiologically and/or histologically confirmed tumor recurrence. Endpoint or duration of follow-up: until death/NR Number of events/outcomes: NR **RESULTS** Multivariable model: *Local Recurrence, coefficient (95% CI)* Gender Male 1 Female 0.698 (0.529 0.921) Grading G2 1 G3 0.816 (0.598 1.113) Tumor size 1.026 (1.004 1.049) Margins R0 1 R1/R2 2.761 (2.021 3.774) Histology Myxoid Liposarcoma 1 MPNST 4.227 (1.837 9.729) Myxofibrosarcoma 4.156 (2.056 8.400) Synovial Sarcoma 3.116 (1.429 7.014) UPS 3.373 (1.620 7.025)	<u>Interpretation</u>: confirmatory, i.e. model useful for practice versus exploratory, i.e. more research needed. <u>Authors' conclusion</u> In conclusion, the present study provides a model to individually predict patient's LR and DM risks during follow-up, applying a flexible parametric competing risk regression approach. These models are at the moment being included in the updated version of the PERSARC app for Individualized Sarcoma Care and follow-up. Although a risk-threshold of 4% for LR and 2% for DM was chosen in the present study, the "optimal" threshold upon which an individual patient should undergo imaging with MRI, chest-CT, or CXR, is still subjected to experts' opinion and should be further discussed with patients concerned.

	Conflicts of Interest: Author van de Sande reports grants from Daiichi Sankyo, outside the submitted work. The remaining authors (Maria A Smolle, Dario Callegaro, JayWunder, Andrew J. Hayes, Lukas Leitner, Marko Bergovec, Per-Ulf Tunn, Veroniek van Praag, Marta Fiocco, Joannis Panotopoulos, Madeleine Willegger, Reinhard Windhager, Sander Djikstra, Winan J van Houdt, Jakob M Riedl, Michael Stotz, Armin Gerger, Martin Pichler, Herbert Stöger, Bernadette Liegl-Atzwanger, Josef Smolle, Dimosthenis Andreou, Andreas Leithner, Alessandro Gronchi, Rick L. Haas, and Joanna Szkandera) have no conflicts of interest to declare.	administered in case a high risk of LR or DM had been anticipated by the multidisciplinary tumor board, according to locally preferred guidelines, LR was defined as a radiologically and/or histologically confirmed tumor recurrence. Participants: Development cohort (DC) N=1,931 Validation cohort (VC) N=1,085 Median age (IQR): DC: 59 years (44.7 to 70) VC: 61 years (47 to 74) Sex: % M / % F DC: 53.8/46.2 VC: 56.7/43.3			Angiosarcoma/Vascular Sarcoma 3.316 (0.981 12.341) Dedifferentiated/Pleomorphic Liposarcoma 1.727 (0.719 4.143) Leiomyosarcoma 2.779 (1.294 5.966) Others 2.385 (1.123 5.065) Neoadjuvant RTX No 1 Yes 0.298 (0.178 0.494) Adjuvant RTX No 1 Yes 0.603 (0.447 0.814) Adjuvant CTX No 1 Yes 1.711 1.154 2.538 Restricted cubic spline 1 2.104 (1.851 2.392) Restricted cubic spline 2 1.332 (1.230 1.442) Restricted cubic spline 3 0.980 (0.937 1.026) Restricted cubic spline for time-dependent effect of grading 0.944 (0.813 1.096) Constant 0.048 (0.024 0.097) Alternative presentation of final model: models included in the updated version of the PERSARC app for Individualized Sarcoma Care and follow-up.	
Rueten-Budde 2018 *Development and internal validation of*	Source of data and date: Clinical data were collected between January 1st, 2000 and December 31st,	Recruitment method: consecutive Inclusion criteria: Patients were selected from each hospital's own	In the following, baseline and time-dependent variables that were included into the dynamic model are defined. Predictors measured at	**Development** Modelling method: proportional landmark supermodel, backward selection procedure **Performance**	Type of outcome: single (dynamic) Definition and method for measurement of outcome: Dynamic overall survival,	Interpretation: confirmatory Authors' conclusion The presence of time-varying effects, as well as the effect of local recurrence and distant

dynamic PERSARC model	2014, at 14 different international specialized sarcoma centers. Setting/ number of centres and country: Included centers are Leiden University Medical Center (Leiden, the Netherlands), Royal Orthopaedic Hospital (Birmingham and Stanmore, UK), Netherlands Cancer Institute (Amsterdam, the Netherlands), Mount Sinai Hospital (Toronto, Canada), the Norwegian Radium Hospital (Oslo, Norway), Aarhus University Hospital (Aarhus, Denmark), Skane University Hospital (Lund, Sweden), and Medical University Graz (Graz, Austria). Funding and conflicts of interest: This work has been supported by the Dutch Cancer Society (DCS) – KWF Kankerbestrijding [UL2015-8028]. The	sarcoma registry based on histological diagnosis. Eligible diagnoses included high-grade (FNCLCC grade II and III [11]) angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma, liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma (MFH/UPS), (pleomorphic) soft tissue sarcomas not-otherwise-specified (NOS), malignant rhabdoid tumor, alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, rhabdomyosarcoma (adult form) and conventional fibrosarcoma. Exclusion criteria: Patients were excluded if they were initially treated without curative intent, presented with LR or DM, had Kaposi's or rhabdomyosarcoma (pediatric form), had a tumor in their abdomen, thorax, head or neck, or	baseline were: age (years), tumor size by the largest diameter measured at pathological examination (centimeters), tumor depth in relation to investing fascia (deep/superficial), and histological subtype according to WHO classification . Radiotherapy (yes/no) was further specified as being either neoadjuvant or adjuvant treatment. Chemotherapy was not included in the model because it was seldom given to patients for primary tumors. Surgical margins were categorized according to the categorical R-system: 'R0' for a negative margin and 'R1-2' for a positive margin with tumor cells in the inked surface of the resection margin. The potential effect modifier grade was not included, since all included patients had high-grade tumors. Local recurrence was defined as the presence of pathologically and/or radiologically confirmed tumor at the site where it was originally detected, more than two months after primary surgery.	Calibration measures and 95%CI: Good model calibration was indicated by a heuristic shrinkage factor equal to 0.996. Discrimination measures and 95%CI: The discriminative ability of the model was measured with dynamic cross-validated C-indices of 0.694, 0.777, 0.813, 0.810, 0.798, and 0.781 at 0-, 1-, 2-, 3-, 4-, and 5-years after surgery respectively. Classification measures: NR **Evaluation** Method for testing model performance: Internal validation	defined as time from surgery to death from any cause or last recorded follow-up; dynamic probability of surviving an additional five years from a prediction time point t_p called dynamic overall survival (DOS). Endpoint or duration of follow-up: until death/NR Number of events/outcomes: Median follow-up of 6.42 years (95% confidence interval: 6.17–6.72). In total 1034 patients died, 143 patients developed LR, 556 DM, and 159 developed both. **RESULTS** Multivariable model: Coefficients: HR (95% CI) *Covariates with time-constant effects* Age (ref: 60 years, per 10 years) Age 1.444 (1.381–1.510) Age^2 1.065 (1.048–1.082) Tumor size (ref: 0 cm, per 1 cm) Size 1.120 (1.072–1.169) Size^2 0.997 (0.996–0.999) Tumor depth (superficial vs. deep) 0.784 (0.654–0.940) Radiotherapy (RT)	metastases on survival, suggest the importance of updating predictions during follow-up. This newly developed dynamic prediction model which updates survival probabilities over time can be used to make better individualized treatment decisions based on a dynamic assessment of a patient's prognosis.

	funding source had no role in the design of this study, execution, analyses, interpretation of the data, report writing or decision to submit the article for publication. Authors Rueten-Budde, van Praag and Fiocco have nothing to disclose. Author van de Sande reports grants from Daiichi Sankyo, outside the submitted work	received isolated limb perfusion as (neo-) adjuvant treatment. Treatment: All patients underwent surgery. Radiotherapy (%) • No radiotherapy 916 (41.0) • Neoadjuvant 265 (11.9) • Adjuvant 1004 (45.0) • Unknown 47 (2.1) Chemotherapy (%) • No chemotherapy 1876 (84.1) • Neoadjuvant 98 (4.4) • Adjuvant 228 (10.2) • Unknown 30 (1.3) Participants: N=2,232 Mean age: 60.86 (SD 18.74) Sex: % M / % F 53.9/46.1	Distant metastases were defined as radiological evidence of systemic spread of tumor distant from the primary tumor site.		No RT 1 Neoadjuvant 0.773 (0.572–1.044) Adjuvant 0.903 (0.763–1.068) Local recurrence (yes vs. no) 1.998 (1.622–2.461) Distant metastasis (yes vs. no) 7.572 (6.501–8.818) *Covariates with time-varying effects* Prediction time (ref: time of surgery, per year) t_p 0.431 (0.330–0.562) t_{p2} 1.127 (1.066–1.192) Histology Constant Myxofibrosarcoma 1 MPNST 1.807 (1.270–2.571) Synovial sarcoma 1.323 (0.971–1.801) Sarcoma – NOS 1.181 (0.784–1.781) Spindle cell sarcoma 0.819 (0.638–1.051) MFH/UPS 1.000 (0.789–1.269) Other 1.229 (0.828–1.825) Histology Linear time-varying effect Myxofibrosarcoma 1 MPNST 0.916 (0.692–1.212) Synovial sarcoma 1.368 (1.084–1.727) Sarcoma – NOS 1.067 (0.739–1.540) Spindle cell sarcoma 1.184 (0.959–1.461) MFH/UPS 1.256 (1.024–1.540) Other 1.050 (0.742–1.486)	

					Histology Quadratic time-varying effect Myxofibrosarcoma 1 MPNST 0.985 (0.930–1.044) Synovial sarcoma 0.913 (0.864–0.964) Sarcoma – NOS 0.983 (0.913–1.058) Spindle cell sarcoma 0.990 (0.947–1.035) MFH/UPS 0.968 (0.928–1.010) Other 0.985 (0.913–1.062) Margin Constant R0 vs. R1-2 0.764 (0.606–0.964) Margin Linear time-varying effect R0 vs. R1-2 1.417 (1.127–1.783) Margin Quadratic time-varying effect R0 vs. R1-2 0.947 (0.902–0.993) Alternative presentation of final model: The results of this study will be made freely available through the updated PERsonalized SARcoma Care (PERSARC) mobile application.	
Rueten-Budde 2021 *Update and external validation of dynamic PERSARC model*	Source of data and date: The model development data were augmented for the update and contained data from Leiden University	Recruitment method: consecutive Inclusion criteria: Selection and exclusion criteria were identical for the model development (update)	The dynamic prediction model developed in Rueten-Budde (2018) was revised by adding more patients and the variable grade to the model.	**Development** Modelling method: N/A **Performance** Calibration measures and 95%CI: VC: calibration plot, author concluded that the figure shows they are relatively close to the diagonal line implying that	Type of outcome: single (dynamic) Definition and method for measurement of outcome: The outcome of interest was OS, defined as the time from surgery to death due to any	Interpretation: confirmatory Authors' conclusion Results from the external validation show that the dynamic PERSARC model is reliable in predicting the probability of surviving an

	Medical Center, Royal Orthopaedic Hospital, Netherlands Cancer Institute, Mount Sinai Hospital, the Norwegian Radium Hospital, Aarhus University Hospital, Skåne University Hospital, Medical University Graz, Royal Marsden Hospital, Erasmus MC Cancer Institute, Radboud University Medical Center, University Medical Center Groningen, Haukeland University Hospital, Helios Klinikum Berlin-Buch, MedUni Vienna, Vienna General Hospital, and the EORTC trial 62931, a randomized controlled trial which studied the effect of intensive adjuvant chemotherapy on several outcome measures. External data were provided by Istituto Nazionale dei Tumori. For both, the model development and external cohort data were collected from	cohort and the external cohort. Included eSTS subtypes included high-grade (FNCLCC Grades II and III) angiosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, spindle cellsarcoma, myxofibrosarcoma, liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, (pleomorphic) soft tissue sarcomas not-otherwise-specified, epithelioid sarcoma, clear cell sarcoma, rhabdomyosarcoma (adult form), conventional fibrosarcoma, giant cell sarcoma, malignant granular cell tumor, unclassified soft tissue sarcoma, and undifferentiated sarcoma. Exclusion criteria: Patients were excluded if they were initially treated without curative intent, presented with LR or DM, had Kaposi's or rhabdomyosarcoma (pediatric form), had		predictions are accurate; the model generally slightly underestimated survival. Discrimination measures and 95%CI: VC: The discriminative ability of the model was assessed with dynamic C-indices, with values equal to 0.697, 0.790, 0.822, 0.818, 0.812, and 0.827 at 0, 1, 2, 3, 4, and 5 years after surgery respectively. Classification measures: NR **Evaluation** Method for testing model performance: External validation	cause or last recorded follow-up. The dynamic model predicts 5-year dynamic overall survival (DOS) from a particular prediction time point during follow-up. Endpoint or duration of follow-up: until death/NR Number of events/outcomes: UC: median follow-up equal to 6.00 years (95% confidence interval [CI] = 5.86–6.18) VC: median follow-up equal to 6.89 years (95% CI = 6.47–7.61). In the development cohort (update), in total 1602 patients died, 241 patients developed LR, 949 DM, and 385 developed both. In the external cohort, 306 patients died, 70 had LR, 279 DM, and 77 developed both. **RESULTS** Multivariable model: Revised model reported. Alternative presentation of final model: The updated dynamic prediction models is implemented in the updated PERSARC application; available for free at the Apple Store and Google Play Store.	additional 5 years from a specific prediction time point during follow-up. The model combines patient-, treatment-specific and time-dependent variables such as local recurrence and distant metastasis to provide accurate survival predictions throughout follow-up and is available through the PERSARC app.

	centers between January 1, 2000, and December 31, 2014. Data from the EORTC trial 62931, which is part of the development cohort, were collected between February 1995, and December 2003. Setting/ number of centres and country: see above Funding and conflicts of interest: ACKNOWLEDGMENT This study has been supported by the Dutch Cancer Society (DCS) – KWF Kankerbestrijding (Grant no. UL2015-8028). The funding source had no role in the design of this study, execution, analyses, interpretation of the data, report writing, or decision to submit the article for publication. CONFLICT OF INTERESTS Authors Anja J. Rueten-Budde, Veroniek M. van Praag, and Marta	tumor in their abdomen, thorax, head, or neck, or received isolated limp perfusion as (neo-) adjuvant treatment. Treatment: All patients underwent resection. Radiotherapy (%) No radiotherapy UC: 1331 (34.8) VC: 474 (42.7) Neoadjuvant UC: 517 (13.5) VC: 138 (12.4) Adjuvant UC: 1878 (49.1) VC: 499 (44.9) Unknown UC: 100 (2.6) VC: 0 (0.0) Chemotherapy (%) No UC: 3189 (83.4) VC: 739 (66.5) Yes UC: 470 (12.3) VC: 372 (33.5) Unknown UC: 167 (4.4) VC: 0 (0.0) Participants: Update cohort (UC) N=3,826 Validation cohort (VC) N=1,111 Mean age (SD): UC: 59.40 (18.10) VC: 55.46 (17.03)				

	Fiocco have nothing to disclose. Author Michiel A. J. van de Sande reports grants from Daiichi Sankyo, outside the submitted work.	Sex: % M / % F UC: 52.6/43.9 (3.5 unknown) VC: 54.6/45.4				

Risk of bias table

Study reference (first author, year of publication) Classification[1]	**Participant selection** 1) Appropriate data sources?[2] 2) Appropriate in- and exclusion? Risk of bias: low/high/unclear	**Predictors** 1) Assessed similar for all participants? 2) Assessed without knowledge of outcome? 3) Available at time the model is intended to be used? Risk of bias: low/high/unclear	**Outcome** 1) Pre-specified or standard outcome definition? 2) Predictors excluded from definition? 3) Assessed similar for all participants? 4) Assessed without knowledge of predictors? 5) Time interval between predictor and outcome measurement appropriate? Risk of bias: low/high/unclear	**Analysis** 1) Reasonable number of participants with event/outcome? 2) All enrolled participants included in analysis? 3) Missing data handled appropriately? 4) No selection of predictors based on univariate analysis? 5) Relevant model performance measures evaluated appropriately?[3] 6) Accounted for model overfitting[4] and optimism? 7) Predictors and weights correspond to results from multivariate analysis? Risk of bias: low/high/unclear	**Overall judgment** *High risk of bias: at least one domain judged to be at high risk of bias.* *Model development only: high risk of bias.* Risk of bias: low/high/unclear
MSKCC; Kattan, 2002; Eilber, 2004; Mariani, 2005; Squires 2022; development and external validation of model	Low (Data obtained from databases in which patients were prospectively entered, consecutive patients or all patients who underwent resection of primary extremity STS in different centers during time period. Clear in- and exclusion criteria)	Unclear, probably high (Clear definitions of predictors. Patients from multiple centers, predictors may have been recorded differently at different centers. Predictors recorded before the outcome occurred.)	Unclear, probably low (Outcome is sarcoma-specific death, may be misclassified. No information on whether assessor of outcome was aware of predictors.)	High (Patients with missing values were excluded (n=139); and for other studies no information on missing data. No effect sizes reported for the predictors in the developed nomogram.)	High risk of bias
SAM; Sampo 2012; development and external validation of model	Unclear, probably low (For development: all patients referred to STS Sarcoma Group in time period, data probably obtained from register but not explicitly described. Data for validation cohort obtained from hospital database. Both with clear in- and exclusion criteria)	Unclear, probably low (Predictors are clearly defined and assessed in the same way for all study participants. Predictors were recorded before the outcome occurred. Not explicitly reported whether re-evaluation/re-assessment was blinded.)	Unclear, probably low (Outcome sarcoma-specific survival, may be misclassified. No information on whether assessor of outcome was aware of predictors.)	High (Missing data for 84 patients in development cohort, patients excluded. Validation cohort: 224 patients excluded, unclear how many due to missing data; “patients with metastatic disease at presentation, patients receiving adjuvant chemotherapy and patients with missing data on the assessed	High risk of bias

				and reported parameters were excluded")	
Sarculator; Callegaro, 2016; Callegaro, 2019; Squires, 2022; Voss, 2022; development and external validation of model	Low (Data obtained from institutional or national prospectively maintained databases. Clear in- and exclusion criteria)	Unclear (Predictors are clearly defined and assessed in the same way for all study participants. Predictors recorded before outcome. Squires: Patients from multiple centers, predictors may have been recorded differently at different centers. Voss: data from national database; predictors may have been recorded differently at different centers.)	Low (Outcome is overall survival, not likely to be misclassified. No information on whether assessor of outcome was aware of predictors.)	Unclear (No information on missing data for Callegaro 2016 and Squires. Callegaro 2019; 12 patients excluded because survival time was missing, small percentage of the total of 3,740. Voss: patients excluded with incomplete grade, treatment, or survival data, not mentioned how many.)	Some concerns
PERSARC; Van Praag, 2017; Smolle, 2019; Rueten-Budde, 2018; Rueten-Budde, 2021; development and external validation of model	Low (Data obtained from prospective sarcoma databases. Clear in- and exclusion criteria)	Unclear	Low (Outcome overall survival is not likely to be misclassified. Outcome local recurrence, clear definition, misclassification not likely. No information on whether assessor of outcome was aware of predictors.)	Unclear Van Praag: Due to missing values for 72 patients, 766 individuals were included	Some concerns

Table of excluded studies

Reference	Reason for exclusion
Anaya, D.A.; Lahat, G.; Wang, X.; Xiao, L.; Pisters, P.W.; Cormier, J.N.; Hunt, K.K.; Feig, B.W.; Lev, D.C.; Pollock, R.E. Postoperative nomogram for survival of patients with retroperitoneal sarcoma treated with curative intent. Ann. Oncol. 2010, 21, 397–402.	model only internally validated
Ardoino I, Miceli R, Berselli M, et al. Histology-specific nomogram for primary retroperitoneal soft tissue sarcoma. Cancer 2010;116:2429-36.	wrong type of STS (RPS)
Cahlon O, Brennan MF, Jia X, Qin LX, Singer S, Alektiar KM. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limbsparing surgery without adjuvant radiation. Ann Surg. 2012;255(2):343–347	model not externally validated
Callegaro, D.; Barretta, F.; Swallow, C.J.; Strauss, D.C.; Bonvalot, S.; Honorè, C.; Stoeckle, E.; van Coevorden, F.; Haas, R.; Rutkowski, P.; et al. Longitudinal prognostication in retroperitoneal sarcoma survivors: Development and external validation of two dynamic nomograms. Eur. J. Cancer 2021, 157, 291–300	wrong type of STS (RPS)
Canter, R.J.; Qin, L.X.; Maki, R.G.; Brennan, M.F.; Ladanyi, M.; Singer, S. A synovial sarcoma-specific preoperative nomogram supports a survival benefit to ifosfamide-based chemotherapy and improves risk stratification for patients. Clin. Cancer Res. 2008, 14, 8191–8197	model only internally validated
Chisholm, J.C.; Marandet, J.; Rey, A.; Scopinaro, M.; de Toledo, J.S.; Merks, J.H.; O0Meara, A.; Stevens, M.C.; Oberlin, O. Prognostic factors after relapse in nonmetastatic rhabdomyosarcoma: A nomogram to better define patients who can be salvaged with further therapy. J. Clin. Oncol. 2011, 29, 1319–1325	wrong type of STS (not primary), wrong population (children)
Crago, A.M.; Denton, B.; Salas, S.; Dufresne, A.; Mezhir, J.J.; Hameed, M.; Gonen, M.; Singer, S.; Brennan, M.F. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann. S	model only internally validated
Dalal, K.M.; Kattan, M.W.; Antonescu, C.R.; Brennan, M.F.; Singer, S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann. Surg. 2006, 244, 381–391.	model only internally validated
Gronchi, A.; Miceli, R.; Shurell, E.; Eilber, F.C.; Eilber, F.R.; Anaya, D.A.; Kattan, M.W.; Honoré, C.; Lev, D.C.; Colombo, C.; et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: Histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. J. Clin. Oncol. 2013, 31, 1649–1655.	wrong type of STS (RPS)

Pasquali, S.; Palmerini, E.; Quagliuolo, V.; Martin-Broto, J.; Lopez-Pousa, A.; Grignani, G.; Brunello, A.; Blay, J.Y.; Tendero, O.; Diaz-Beveridge, R.; et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: A Sarculator-based risk stratification analysis of the ISG-STS 1001 randomized trial. Cancer 2022, 128, 85–93. Erratum in Cancer 2022, 128, 3265.	different type of research question (added value of chemotherapy)
Raut, C.P.; Callegaro, D.; Miceli, R.; Barretta, F.; Rutkowski, P.; Blay, J.Y.; Lahat, G.; Strauss, D.C.; Gonzalez, R.; Ahuja, N.; et al. Predicting Survival in Patients Undergoing Resection for Locally Recurrent Retroperitoneal Sarcoma: A Study and Novel Nomogram from TARPSWG. Clin. Cancer Res. 2019, 25, 2664–2671	model only internally validated
Sekimizu M, Ogura K, Yasunaga H, et al. Development of nomograms for prognostication of patients with primary soft tissue sarcomas of the trunk and extremity: report from the Bone and Soft Tissue Tumor Registry in Japan. BMC Cancer. 2019;19(1):657	model only internally validated
Shen, W.; Sakamoto, N.; Yang, L. Model to predict the survival benefit of radiation for patients with rhabdomyosarcoma after surgery: A population-based study. Int. J. Oncol. 2014, 45, 549–557	model only internally validated
Tan, M.C.; Brennan, M.F.; Kuk, D.; Agaram, N.P.; Antonescu, C.R.; Qin, L.X.; Moraco, N.; Crago, A.M.; Singer, S. Histology-based Classification Predicts Pattern of Recurrence and Improves Risk Stratification in Primary Retroperitoneal Sarcoma. Ann. Surg. 2016, 263, 593–600	model only internally validated
Tan, P.H.; Thike, A.A.; Tan, W.J.; Thu, M.M.; Busmanis, I.; Li, H.; Chay, W.Y.; Tan, M.H.; Phyllodes Tumour Network Singapore. Predicting clinical behaviour of breast phyllodes tumours: A nomogram based on histological criteria and surgical margins. J. Clin. Pathol. 2012, 65, 69–76	article not available
Tu Q, Hu C, Zhang H, et al. Development and validation of novel nomograms for predicting specific distant metastatic sites and overall survival of patients with soft tissue sarcoma. Technol Cancer Res Treat. 2021;20:1533033821997828.	model not externally validated (not in a separate population)
Xu Y, Xu G, Wu H, et al. The nomogram for early death in patients with bone and soft tissue tumors. J Cancer. 2020;11(18):5359–5370	model only internally validated
Yang, L.; Takimoto, T.; Fujimoto, J. Prognostic model for predicting overall survival in children and adolescents with rhabdomyosarcoma. BMC Can	model only internally validated
Zhang SL, Wang ZM, Wang WR, Wang X, Zhou YH. Novel nomograms individually predict the survival of	model not externally validated (not in a separate population)

patients with soft tissue sarcomas after surgery. Cancer Manag Res. 2019;11:3215–3225	
Zivanovic, O.; Jacks, L.M.; Iasonos, A.; Leitao, M.M., Jr.; Soslow, R.A.; Veras, E.; Chi, D.S.; Abu-Rustum, N.R.; Barakat, R.R.; Brennan, M.F.; et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. Cancer 2012, 118, 660–669	model only internally validated

Zoekverantwoording

Algemene informatie

Richtlijn: NVVH wekedelentumoren	
Uitgangsvraag: Which model predicts *overall survival and local recurrence* in patients from patients with soft tissue sarcoma and what is the predictive value of this model?	
Database(s): Ovid/Medline, Embase	Datum: 12-6-2023, 12-10-2023
Periode: vanaf 2010	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp en Esther van der Bijl	

Zoekopbrengst

12-10-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.o.v. Rayyan 12-6-2023**
SRs	68	22	12
RCTs	157	49	167
Observationele studies	715	286	783
Totaal	940	357	962
Totaal in Rayyan			**1178**
12-6-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	189	79	216
RCTs			
Observationele studies			
Totaal			**216**

Zoekstrategie Embase 12-10-2023

No.	**Query**	**Results**
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp	108300

	OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)	
#2	'mortality'/exp OR 'survival'/exp OR 'cancer survivor'/exp OR 'recurrent disease'/exp OR 'metastasis'/exp OR 'prognosis'/exp OR mortal*:ti,ab,kw OR death:ti,ab,kw OR surviv*:ti,ab,kw OR relaps*:ti,ab,kw OR metasta*:ti,ab,kw OR prognos*:ti,kw	6043181
#3	#1 AND #2	49186
#4	'area under the curve'/exp OR 'brier score'/exp OR 'computer prediction'/exp OR 'c statistic'/exp OR 'c statistics'/exp OR 'integrated discrimination improvement'/exp OR 'net reclassification improvement'/exp OR 'net reclassification index'/exp OR 'prediction'/exp OR 'predictive model'/exp OR 'predictive modeling'/exp OR 'predictive validity'/exp OR 'predictive value'/exp OR 'regression analysis'/exp OR 'statistical model'/exp OR 'area under the curve':ti,ab,kw OR 'brier score*':ti,ab,kw OR 'c statistic*' OR 'computer prediction':ti,ab,kw OR 'decision curve anal*':ti,ab,kw OR (('net reclassification' NEAR/2 (improvement OR index)):ti,ab,kw) OR (((predict* OR statistical*) NEAR/3 (model* OR validity OR value)):ti,ab,kw) OR 'proportional hazards model*':ti,ab,kw OR 'r square*':ti,ab,kw OR regression:ti,ab,kw OR predict*:ti OR multivariate:ti,ab,kw OR multivariab*:ti,ab,kw OR sarculator:ti,ab,kw OR nomogram*:ti,ab,kw OR persarc:ti,ab,kw	3322253
#5	#3 AND #4	5910
#6	#5 AND [2021-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1023
#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de	1621953

	OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab OR 'practice guideline'/exp	
#8	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3891716
#9	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	7878511
#10	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1	14490235

	(blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#11	#6 AND #7 **– SR's**	68
#12	#6 AND #8 NOT #11 – **RCT's**	157
#13	#6 AND (#9 OR #10) NOT #11 NOT #12 **- Observationeel**	715
#14	#11 OR #12 OR #13	940

Zoekstrategie Ovid/Medline 12-10-2023

#	Searches	Results
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve	64525

	sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf.	
2	exp prognosis/ or exp Mortality/ or Survival/ or exp Cancer Survivors/ or Neoplasm Recurrence, Local/ or Recurrence/ or exp Neoplasm Metastasis/ or mortal*.ti,ab,kf. or death.ti,ab,kf. or surviv*.ti,ab,kf. or relaps*.ti,ab,kf. or metasta*.ti,ab,kf. or prognos*.ti,kf.	4930606
3	1 and 2	28677
4	limit 3 to yr="2021 -Current"	3999
5	Area Under Curve/ or exp Forecasting/ or "Predictive Value of Tests"/ or exp Multivariate Analysis/ or exp Regression Analysis/ or exp Models, Statistical/ or area under the curve.ti,ab,kf. or brier score*.ti,ab,kf. or c statistic*.ti,ab,kf. or computer prediction.ti,ab,kf. or decision curve anal*.ti,ab,kf. or (net reclassification adj2 (improvement or index)).ti,ab,kf. or ((predict* or statistical*) adj3 (model* or validity or value)).ti,ab,kf. or proportional hazards model*.ti,ab,kf. or r square*.ti,ab,kf. or regression.ti,ab,kf. or predict*.ti. or multivaria*.ti,ab,kf.	2470299
6	4 and 5	696
7	6 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	685
8	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	699046
9	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1652711

10	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4551561
11	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5529373
12	7 and 8 **– SR's**	22
13	(7 and 9) not 12 **– RCT's**	49
14	10 and 11	2704733
15	(7 and 14) not (12 or 13) **- Observationeel**	286
16	12 or 13 or 15	357

Module 4.1 – Type chirurgie

Search and select
A systematic review of the literature was performed to answer the following question: What is the effectivity and safety of compartmental resection compared with wide excision or wide local excision in patients with soft tissue sarcoma?

P	**(patients)**	: patients with extremity soft tissue sarcomas
I	**(intervention)**	: compartmental resection
C	**(comparison)**	: wide excision or wide local excision (WLE)
O	**(outcomes)**	: overall survival, local recurrence, quality of life/morbidity

Relevant outcome measures
The guideline development group considered overall survival as a critical outcome measure for decision making, as well as local recurrence, and quality of life/morbidity as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the minimal clinically (patient) important differences for the outcomes overall survival based on the PASKWIL criteria (NVMO, 2023), and for the other outcomes based on relevant literature:

- Overall survival: 5% or 3% and Hazard Ratio (HR) <0.7 (median follow-up > 3 years).
- Local recurrence: 25% difference, RR <0.8 or >1.25
- Quality of life/morbidity: The minimum important difference (MID) has been estimated to be a difference of 0.08 or more points for the EQ-5D utility index and seven or more points for the EQ-5D VAS (Pickard, 2007). For quality of life measured with the EORTC QLQ-C30, a difference of 10 points was considered as a clinical important difference (Fiteni, 2016)

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2015 until 21 September 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1256 hits. Studies were selected based on the following criteria:

- Study design: randomized controlled trial, systematic review or observational study.
- Adult patients with extremity soft tissue sarcoma undergoing surgery, comparing compartmental resection with wide excision or wide local excision
- Describing at least one of the relevant outcomes specified in the PICO.

Fifteen studies were initially selected based on title and abstract screening. After reading the full text, 15 studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included. Subsequently, the references of the ESMO EURACAN GENTURIS Clinical Practice Guidelines (2021) were searched for additional relevant studies published before 2015. As a result, no additional studies were included.

Results
No studies were included in the analysis of the literature.

Summary of literature

Description of studies

No studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

Results

Overall survival

No results could be reported as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

Local recurrence

No results could be reported as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

Quality of life/morbidity

No results could be reported as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

Level of evidence of the literature

The level of evidence regarding the outcome measure **overall survival** could not be graded as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

The level of evidence regarding the outcome measure **local recurrence** could not be graded as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

The level of evidence regarding the outcome measure **quality of life/morbidity** could not be graded as no studies reporting the impact of compartmental resection compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas were found.

Conclusions

No GRADE	No evidence was found regarding the effect of compartmental resection on **overall survival** compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas. *Source: -*

No GRADE	No evidence was found regarding the effect of compartmental resection on **local recurrence** compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas. *Source: -*

No GRADE	No evidence was found regarding the effect of compartmental resection compared with wide excision or wide local excision on **quality of life/morbidity** compared with wide excision or wide local excision in patients with extremity soft tissue sarcomas.

	Source: -

Kennislacunes

What is the effectivity and safety of compartmental resection compared with wide excision or wide local excision in patients with soft tissue sarcoma?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	Geen nieuwe behandelvormen voorgesteld	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Table of excluded studies

Reference	Reason for exclusion
Jang WY, Kim HS, Han I. Impact of surgical margin on survival in extremity soft tissue sarcoma: A systematic review and meta-analysis. Medicine (Baltimore). 2021 Jan 22;100(3):e24124. doi: 10.1097/MD.0000000000024124. PMID: 33546021; PMCID: PMC7837970.	Different research question (effect of margins)

Boughzala-Bennadji R, Stoeckle E, Le Péchoux C, Méeus P, Honoré C, Attal J, Duffaud F, De Pinieux G, Bompas E, Thariat J, Leroux A, Bertucci F, Isambert N, Delcambre C, Blay JY, Sunyach MP, Coindre JM, Sargos P, Penel N, Bonvalot S. Localized Myxofibrosarcomas: Roles of Surgical Margins and Adjuvant Radiation Therapy. Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):399-406. doi: 10.1016/j.ijrobp.2018.05.055. Epub 2018 Jun 2. PMID: 30191871.	Wrong tumor type: myxofibrosaroma
Chen YT, Tu WT, Lee WR, Huang YC. The efficacy of adjuvant radiotherapy in dermatofibrosarcoma protuberans: a systemic review and meta-analysis. J Eur Acad Dermatol Venereol. 2016 Jul;30(7):1107-14. doi: 10.1111/jdv.13601. Epub 2016 Feb 16. PMID: 26879523.	Different research question (effect adjuvant radiotherapy)
Gallaway KE, Ahn J, Callan AK. Thirty-Day Outcomes after Surgery for Primary Sarcomas of the Extremities: An Analysis of the NSQIP Database. J Oncol. 2020 Jan 13;2020:7282846. doi: 10.1155/2020/7282846. PMID: 32411242; PMCID: PMC7201584.	Wrong study design: case series
Hasley I, Gao Y, Blevins AE, Miller BJ. The Significance of a "Close" Margin in Extremity Sarcoma: A Systematic Review. Iowa Orthop J. 2018;38:123-130. PMID: 30104934; PMCID: PMC6047382.	Different research question (margin classifications)
Heer J, Allison DC, Helmstedter CS. Factors, treatments, and outcomes associated with primary soft tissue malignancies of the forearm: A series of 31 cases. J Orthop. 2021 Nov 11;28:58-61. doi: 10.1016/j.jor.2021.11.001. PMID: 34840483; PMCID: PMC8605106.	Wrong study design (case series)
Hoefkens F, Dehandschutter C, Somville J, Meijnders P, Van Gestel D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. Radiat Oncol. 2016 Oct 12;11(1):136. doi: 10.1186/s13014-016-0668-9. PMID: 27733179; PMCID: PMC5062836.	Wrong study design (no sustematic review)
Hong AM, Sundaram A, Perianayagam G, Lo H, Lawless A, Zhou D, McDonough J, Thompson SR, Maclean F, Connolly EA, Coker D, Mar J, Lazarakis S, Johnston A. Surgery at specialised sarcoma centres improves patient outcomes - A systematic review by the Australia and New Zealand sarcoma association clinical practice guidelines working party. Eur J Surg Oncol. 2023 Sep;49(9):106951. doi: 10.1016/j.ejso.2023.06.003. Epub 2023 Jun 7. PMID: 37301636.	Different research question (surgery in specialist vs non-specialist centre)
Jibbe A, Worley B, Miller CH, Alam M. Surgical excision margins for fibrohistiocytic tumors, including atypical fibroxanthoma and undifferentiated pleomorphic sarcoma: A probability model based on a systematic review. J Am Acad Dermatol. 2022	Wrong study design (probabilistic model)

Oct;87(4):833-840. doi: 10.1016/j.jaad.2021.09.036. Epub 2021 Sep 26. PMID: 34587553.	
Kannan S, Chong HH, Chew B, Ferguson JD, Galloway E, McCulloch T, Rankin KS, Ashford RU. Leiomyosarcoma in the extremities and trunk wall: systematic review and meta-analysis of the oncological outcomes. World J Surg Oncol. 2022 Apr 18;20(1):124. doi: 10.1186/s12957-022-02584-4. PMID: 35436892; PMCID: PMC9014567.	Different research question (prognostic factors including tumor margins but not surgery type)
Olson CR, Suarez-Kelly LP, Ethun CG, Shelby RD, Yu PY, Hughes TM, Palettas M, Tran TB, Poultsides G, Tseng J, Roggin KK, Chouliaras K, Votanopoulos K, Krasnick BA, Fields RC, King DM, Bedi M, Pollock RE, Grignol VP, Cardona K, Howard JH. Resection Status Does Not Impact Recurrence in Well-Differentiated Liposarcoma of the Extremity. Am Surg. 2021 Nov;87(11):1752-1759. doi: 10.1177/00031348211054536. Epub 2021 Nov 10. PMID: 34758653.	Wrong comparison (radical vs excisional)
Rastrelli M, Del Fiore P, Damiani GB, Mocellin S, Tropea S, Spina R, Costa A, Cavallin F, Rossi CR. Myoepithelioma of the soft tissue: A systematic review of clinical reports. Eur J Surg Oncol. 2019 Sep;45(9):1520-1526. doi: 10.1016/j.ejso.2019.05.003. Epub 2019 May 6. PMID: 31085025.	Wrong study design (SR of clinical reports)
Saiag P, Grob JJ, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, Peris K, Stratigos A, Middelton M, Basholt L, Testori A, Garbe C. Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline. Eur J Cancer. 2015 Nov;51(17):2604-8. doi: 10.1016/j.ejca.2015.06.108. Epub 2015 Jul 16. PMID: 26189684.	Wrong study design (guideline)
Sambri A, Bianchi G, Cevolani L, Donati D, Abudu A. Can radical margins improve prognosis in primary and localized epithelioid sarcoma of the extremities? J Surg Oncol. 2018 May;117(6):1204-1210. doi: 10.1002/jso.24955. Epub 2017 Dec 19. PMID: 29266231.	Wrong intervention (radical vs non-radical margins)
Wittenberg S, Paraskevaidis M, Jarosch A, Flörcken A, Brandes F, Striefler J, Kaul D, Roohani S, Khakzad T, Märdian S, Rau D. Surgical Margins in Soft Tissue Sarcoma Management and Corresponding Local and Systemic Recurrence Rates: A Retrospective Study Covering 11 Years and 169 Patients in a Single Institution. Life (Basel). 2022 Oct 25;12(11):1694. doi: 10.3390/life12111694. PMID: 36362849; PMCID: PMC9695590.	Wrong intervention (margins instead of surgery type)

Zoekverantwoording

Database(s): Ovid/Medline, Embase	Datum: 26-6-2023, 7-9-2023, 21-9-2023
Periode: 2010-	Talen: nvt

Zoekopbrengst

21-9-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.ov. 7-9 en 26-6 Rayyan**
SRs	110	80	7
RCTs	126	132	133
Observationele studies	674	674	834
Overig			
Totaal			**1256**
7-9-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs			
RCTs			
Observationele studies	100		
Overig			
Totaal			100
	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	133	102	128
RCTs	54	61	54
Observationele studies			
Overig			
Totaal			182

Zoekstrategie

21-9-2023

No.	*Query*	*Results*
#15	*#12 AND (#9 OR #10) NOT #13 NOT #14*	*911*
#14	*#11 AND #12 NOT #13*	*171*
#13	*#5 AND #12*	*140*

#12	*#3 AND [2010-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)*	*2605*
#11	*'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti*	*3877290*
#10	*'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative*	*14430027*

	odds':ab OR 'risk ratio':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))*	
#9	*'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)*	*6767914*
#8	*#4 AND #6*	*64*
#7	*#4 AND #5*	*140*
#6	*'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw*	*1839814*
#5	*'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab*	*733409*
#4	*#3 AND [2010-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)*	*2533*
#3	*#1 AND #2*	*5885*

#2	*'radical resection'/exp OR (((radical OR compartment OR complete OR extensive) NEAR/3 (resection OR excision OR surg*)):ti,ab,kw) OR r0:ti,ab,kw OR '(r0)':ti,ab,kw OR 'no residual tumor':ti,ab,kw OR ((negative NEAR/3 margin*):ti,ab,kw)*	*160409*
#1	*'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)*	*106651*

26-6-2023

Embase

No.	Query	Results
#8	#4 AND #6 NOT #7 RCTs	54
#7	#4 AND #5 SRs	133
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data	733409

	base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#4	#3 AND [2010-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	2533
#3	#1 AND #2	5885
#2	'radical resection'/exp OR (((radical OR compartment OR complete OR extensive) NEAR/3 (resection OR excision OR surg*)):ti,ab,kw) OR r0:ti,ab,kw OR '(r0)':ti,ab,kw OR 'no residual tumor':ti,ab,kw OR ((negative NEAR/3 margin*):ti,ab,kw)	160409
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)	106651

Ovid/Medline

#	Searches	Results
9	(5 and 7) not 8 RCTs	61
8	5 and 6 SRs	102

7	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1619112
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	673116
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	2423
4	limit 3 to yr="2010 -Current"	2483
3	1 and 2	4113
2	"Margins of Excision"/ or ((radical or compartment or complete or extensive) adj3 (resection or excision or surg*)).ti,ab,kf. or r0.ti,ab,kf. or "(r0)".ti,ab,kf. or no residual tumor.ti,ab,kf. or (negative adj3 margin*).ti,ab,kf.	102173
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf.	63646

Module 4.2 – (Neo)adjuvante radiotherapie

Search and select
A systematic review of the literature was performed to answer the following question:
What are the benefits and harms of surgery with (neo)adjuvant radiotherapy compared with surgery only for patients with soft tissue sarcoma?

P (patients)	:	patients with soft tissue sarcoma (patients with soft tissue sarcomas with very low risk of recurrence or easy reoperation)
I (intervention)	:	surgery and radiotherapy
C (comparison)	:	surgery only
O (outcome)	:	local recurrence, overall survival, progression free survival, quality of life, safety

Relevant outcome measures
The guideline development group considered local recurrence as a critical outcome measure for decision making; and overall survival, progression free survival, quality of life, and safety as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the minimal clinically (patient) important differences for the outcomes overall survival, progression free survival, and adverse events based on the PASKWIL criteria (NVMO, 2023), and for the other outcomes based on relevant literature:

- Local recurrence: 25% difference, RR <0.8 or >1.25
- Overall survival: 5% or 3% and Hazard Ratio (HR) <0.7 (median follow-up > 3 years).
- Progression free survival: HR <0.6.
- Safety: adverse events including wound complications, lethal >5%, acute or severe >25%.
- Quality of life: The minimum important difference (MID) has been estimated to be a difference of 0.08 or more points for the EQ-5D utility index and seven or more points for the EQ-5D VAS (Pickard, 2007). For quality of life measured with the EORTC QLQ-C30, a difference of 10 points was considered as a clinical important difference (Fiteni, 2016).

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2015 until 15 May 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search was combined with the search for the module optimal sequence surgery and radiotherapy and resulted in 699 hits. Studies were selected based on the following criteria:

- Study design: randomized controlled trial or systematic review.
- Adult patients with soft tissue sarcoma who underwent surgery combined with radiotherapy vs surgery alone.
- Describing at least one of the relevant outcomes specified in the PICO.

Initially, 39 studies were selected for both modules based on title and abstract screening. After reading the full text, 38 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included for the current module.

Subsequently, the references of the ESMO EURACAN GENTURIS Clinical Practice Guidelines (2021) were searched for additional relevant studies published before 2015. As a result, two additional studies were included.

Results
In total, three studies that described two different trials were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature
Description of studies
Bonvalot (2020) conducted a multicenter open-label randomized phase 3 trial to evaluate the impact of preoperative radiotherapy plus surgery versus surgery alone on abdominal recurrence-free survival in patients with primary retroperitoneal sarcoma. In total, 266 patients were randomly assigned to receive preoperative radiotherapy plus surgery (n=133, intervention group) or surgery alone (n=133, control group).
Baseline characteristics did not differ between intervention and control group. Not all patients received the study treatment as allocated: 119 (89%) patients in the intervention group had both radiotherapy and surgery and 128 (96%) patients from the control group had surgery.
Abdominal recurrence-free survival and overall survival were analyzed in the intention-to-treat population. Safety was analyzed in all patients who started their allocated treatment.

Yang (1998) conducted a randomized, prospective study to assess the impact of postoperative external-beam radiation therapy in patients with extremity soft tissues sarcomas after limb-sparing resection. In total 141 patients were included in the trial. 91 of these included patients had high grade sarcomas and also received adjuvant chemotherapy. For this literature summary we were only interested in patients with low-grade sarcoma who did not receive chemotherapy. A subgroup analysis was performed among 50 patients with low-grade sarcomas was randomized to resection and postoperative adjuvant external beam radiotherapy (=26, intervention group) or resection alone (n=24, control group). There was one patient who refused radiotherapy after randomization; the patient is included in all analyses according to randomization (intention-to-treat analysis).
Baseline characteristics did not differ between intervention and control group. Baseline characteristics did not differ between intervention and control group.
Beane (2014) reported the 20 year follow-up outcomes of the same trial. Since the original publication (Yang, 1998) 55 patients had died (39%), 19 (13%) were lost to follow-up, and 76 (48%) confirmed alive. Of the patients confirmed alive, 54 (71%) completed telephone interviews (Table 2). A total of 22 patients (29 %) did not complete the questionnaire because they were unwilling to participate or were unable to be contacted by telephone and excluded in this follow-up study.

Results
Local recurrence
Yang (1998) reported the number of extremity STS patients with local recurrence (LR) in the two study groups. With a median follow-up of 9.9 years (range 1.4 to 12.4 years) LR was reported for 1 patient in the intervention group and 8 patients in the control group. The RR of 0.12 (95%CI 0.02 to 0.86) is considered clinically relevant in favor of the intervention group.

Bonvalot (2020) reported the outcome abdominal recurrence-free survival (AFRS) in retroperitoneal STS patients. With a median follow-up of 43.1 months (IQR 28.8 to 59·2), 121

abdominal recurrence-free survival events were reported in the two study groups: 60 in the intervention group and 61 in the control group. Corresponding abdominal recurrence-free survival at 3 years was 60.4% (95% CI 51.4 to 68.2) in the intervention group and 58.7% (95% CI 49.5 to 66.7) in the control group. Median abdominal recurrence-free survival was 4.5 years (95% CI 3.9 to not estimable) in the intervention group and 5.0 years (95% CI 3.4 to not estimable) in the control group. The HR was 1.01 (0.71 to 1.44). This is not considered clinically relevant.

Overall survival
Bonvalot (2020) reported overall survival, defined as the time measured from the date of randomization to the date of death. At 3 years the overall survival was 84.0% (95% CI 76.3 to 89.4%) in the intervention group and 84.6% (95% CI 76.5 to 90.1%) in the control group. The difference of -0.6% is not considered clinically relevant.
At 5 years the overall survival was 76.7% (95% CI 66.9 to 84.0%) in the intervention group and 79.4% (95% CI 69.1 to 86.5%) in the control group. The difference of 2.7% is not considered clinically relevant.

Median overall survival was not reached in either group (95% CI not reached to not reached in both groups. The Hazard Ratio (HR) was 1.16 (95% CI 0.5 to 2.05). This is not considered clinically relevant.

Yang (1998) only reported overall survival for the subgroup of patients with high grade sarcomas that also received chemotherapy. For the subgroup of patients with high grade sarcomas it was reported that in both groups 2 patients died from metastatic disease.
Beane (2014) reported overall survival after 10 years and 20 years for the entire study population (both the patients with low grade sarcomas and the patients with high grade sarcomas who also received chemotherapy). The 10-year survival was 82% (95% CI 72 to 90%) in the intervention group and 77% (95% CI 66 to 85%) in the control group. The difference of 5% is considered clinically relevant in favor of the intervention group.

At 20 years, the survival was 71% (95% CI 59 to 81%) in the intervention group compared with 64% (95% CI 52 to 75%) in the control group. The difference of 7% is considered clinically relevant in favor of the intervention group.

No absolute values were reported for the subgroup of patients with low grade sarcomas. Data was only reported graphically in a survival plot, so the information was extracted from the graph. At 10 years, the survival was estimated at 92% in the intervention group compared with 87% in the control group. At 20 years, the survival was 87% in the intervention group compared with 64% in the control group.

Progression-free survival
None of the included studies reported the outcome progression-free survival.

Quality of life
Bonvalot (2020) measured patient-reported quality of life with paper QLQ-C30 questionnaires at baseline, year 1, and year 5. Because compliance was low and data were too sparse to allow any meaningful estimation of treatment differences these results were not reported. Therefore, the clinical relevance cannot be determined.

Yang (1998) used the Functional Living Index–Cancer (FLIC) and performance of activities of daily living (quantitated by the modified Erdman scale) to measure quality of life. Results were

reported only for the entire study population (both the patients with low grade sarcomas and the patients with high grade sarcomas who also received chemotherapy). Mean FLIC -scores per group were reported (see Table 1) but no scores were reported for the Erdman scale. The differences between patients were described as not significant, but no additional data was reported and therefore this cannot be checked.

Table 1 – Mean FLIC-scores per group

Mean FLIC-score (0-154)	baseline	6 months	12 months	24 months	36 months
Intervention group	114	118	129	125	131
Control group	112	125	127	130	127

Safety

Bonvalot (2020) reported the outcome 'safety' that was analyzed in all patients who started their allocated treatment. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.018 during the preoperative period and follow-up period (as of 60 days after surgery). Serious adverse events (not further specified) were reported in 30 (24%) of 127 patients in the intervention group, and in 13 (10%) of 128 patients in the control group. The RR of 2.33 (95%CI 1.27 to 4.25) is considered clinically relevant in favor of the control group.

One (1%) of 127 patients in the intervention group died due to treatment-related serious adverse events (gastropleural fistula), and no patients in the control group died due to treatment-related serious adverse events.

Beane (2014) reported wound complications. In the intervention group 8 of 30 patients (27%; 95% CI 12 to 46%) required wound care or subsequent major surgical interventions compared with 5 of 24 patients (20%; 95% CI 7 to 42%) in the control group. Separate outcome data for the subgroup of patients with low grade sarcomas were not reported.

Level of evidence of the literature

The level of evidence for all outcomes was based on randomized controlled trials and therefore started at high.

Extremity STS

The level of evidence regarding the outcome measure **local recurrence** was downgraded by two levels to **low** because of applicability due to a study population that also included patients with high grade tumors who are at a higher risk of recurrence (indirectness, -1); and the confidence interval crossing the borders of clinical relevance (imprecision, -1).

Retroperitoneal STS

The level of evidence regarding the outcome measure **local recurrence** was downgraded by two levels to **low** because of the confidence interval crossing the borders of clinical relevance (imprecision, -2).

Extremity STS

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of applicability due to a mixed study population with patients who also received chemotherapy (indirectness, -1); and the confidence intervals crossing the border of clinical relevance (imprecision, -1).

Retroperitoneal STS

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of applicability due to a mixed study population with patients with

high grade tumors who are at a higher risk of recurrence (indirectness, -1); and the confidence intervals crossing the border of clinical relevance (imprecision, -1).

As none of the included studies reported quantitative data on **progression free survival,** it was not possible to assess the level of evidence.

As none of the included studies reported quantitative data on **quality of life**, it was not possible to assess the level of evidence.

The level of evidence regarding the outcome measure **safety** was downgraded by three levels to **very low** because of applicability due to a mixed study population with patients who also received chemotherapy (indirectness, -1); and OIS not met (imprecision, -2).

Conclusions

Low GRADE	(Neo)adjuvant radiotherapy may result in an decrease in **local recurrence** in patients with extremity soft tissue sarcomas undergoing surgery in the long term. *Source: Yang, 1998*
Low GRADE	(Neo)adjuvant radiotherapy may result in little or no difference in **local recurrence** in patients with retroperitoneal soft tissue sarcomas undergoing surgery. *Source: Bonvalot, 2020*

Low GRADE	(Neo)adjuvant radiotherapy may result in an increase in **overall survival** in patients with extremity soft tissue sarcomas undergoing surgery in the long term. *Source: Beane 2014*
Low GRADE	(Neo)adjuvant radiotherapy may result in little or no difference **in overall survival** in patients with retroperitoneal soft tissue sarcomas undergoing surgery. *Source: Bonvalot 2020*

NO GRADE	No evidence was found regarding the effect of (neo)adjuvant radiotherapy on **progression free survival** in patients with extremity and retroperitoneal soft tissue sarcomas undergoing surgery. *Source: -*

NO GRADE	No evidence was found regarding the effect of (neo)adjuvant radiotherapy on **quality of life** in patients with extremity and retroperitoneal soft tissue sarcomas undergoing surgery. *Source: -*

Very low GRADE	The evidence is very uncertain for the effect of (neo)adjuvant radiotherapy on **safety** in patients with extremity and retroperitoneal soft tissue sarcomas undergoing surgery. *Source: Bonvalot, 2020; Beane, 2014*

Kennislacunes

What are the favorable and unfavorable effects of surgery with (neo)adjuvant radiotherapy compared with surgery only for patients with soft tissue sarcoma?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
implementatie van PERSARC/SARCULATOR ter beoordeling risico op lokaal recidief en overleving	< 1 jaar	Geen is een gratis applicatie	Gebruik van deze risico modellen zijn richting gevend niet leidend.	Op basis van risico profielen berekend retrospectieve data kunnen geen behandelindicaties of behandeladviezen worden gegeven.	Risico calculatie in MDO en uitslag gesprek met patiënt introduceren	Lokale behandel teams	nvt

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Bonvalot, 2020	Type of study: RCT (open label phase 3 trial) Setting and country: 31 research institutions, hospitals, and cancer centres in Europe (France, Italy, UK, the Netherlands, Norway, Poland, Belgium, Denmark, Sweden, Spain, and Germany, in order of the number of inclusions), Canada, and the USA Funding and conflicts of interest: *Role of the funding source:* EORTC had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. Data were collected by investigators and associated site personnel, analysed by a statistician (SL)	Inclusion criteria: Eligible patients were aged 18 years or older with histologically documented, centrally reviewed, localised, primary soft tissue sarcoma of the retroperitoneal or intraperitoneal spaces of the pelvis. The tumour had to be unifocal; non-metastatic; not previously treated, not extending through the sciatic notch or across the diaphragm; and not originating from bone structure, abdominal, or gynecological viscera; and both operable and suitable for radiotherapy as per evaluation by an institutional multidisciplinary tumour board. A contrast-enhanced chest, abdomen, and pelvis CT scan or MRI scan was required within 28 days before randomisation, with radiologically measurable disease (as	Intervention group: preoperative radiotherapy followed by en-bloc curative-intent surgery: Multivisceral en-bloc curative-intent surgery was done within 4–8 weeks from the end of radiotherapy in the radiotherapy plus surgery group. In the radiotherapy plus surgery group, preoperative radiotherapy was delivered via a 3D conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) technique (including tomotherapy) done according to EORTC quality assurance in radiotherapy (as detailed in the protocol). Radiotherapy was started within 8 weeks	Control group: en-bloc curative-intent surgery alone: Multivisceral en-bloc curative-intent surgery was done within 4 weeks of randomisation in the surgery alone group.	Length of follow-up: Follow-up scans in both groups were planned at 24 weeks after randomisation and every 12 weeks subsequently during the first year, and then every 6 months until recurrence or death. Loss-to-follow-up: Intervention: 14 (10%) Reasons: 8 had radiotherapy, but did not have surgery (1 withdrew consent, 3 had distant metastasis, 1 did not meet operability criteria, 1 had problem with anaesthesia, 2 died before surgery), 4 did not have radiotherapy but had surgery (3	Overall survival At 3 years % (95%CI) I: 84.0% (76.3–89.4) C: 84.6% (76.5–90.1) At 5 years I: 76.7% (66.9–84.0) C: 79.4% (69.1–86.5) and in the radiotherapy plus surgery group overall survival was 84.0% (76.3–89.4) at 3 years and 76.7% (66.9–84.0) at 5 years. Median overall survival was not reached in either group (95% CI not reached to not reached in both groups; HR 1.16, 95% CI 0.65–2.05. Progression-free survival Median abdominal recurrence-free survival: I: 4.5 years (95% CI 3.9 to not estimable) C: 5.0 years (3.4 to not estimable) Hazard ratio: 1.01, 95% CI 0.71–1.44 Local recurrence Not reported.	Author's conclusion: This trial is negative, with similar abdominal recurrence-free survival and overall survival in both groups at 3 years of follow-up. As a consequence, preoperative radiotherapy cannot be considered as the standard of care for retroperitoneal sarcoma.

	working in EORTC headquarters, and interpreted by members of the steering committee. Raw data are available from SL. The corresponding author had the final responsibility for the decision to submit for publication and had full access to all the data. *Declaration of interests*: SB reports personal fees and non-financial support from Nanobiotix and PharmaMar, and non-financial support from Pfizer, outside the submitted work. AG reports personal fees from Novartis, Pfizer, Bayer, Lilly Oncology, SpringWorks, and Nanobiotix, and grants and personal fees from PharmaMar, all outside the submitted work. CLP reports personal fees from AstraZeneca, Amgen, Nanobiotix, Roche, Medscape, PrimeOncology, and Lilly, outside the submitted work. PR reports personal fees	per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Patients were required to have a WHO performance status of 2 or lower; an American Society of Anesthesiologist (ASA) score of 2 or lower; and an absence of history of bowel obstruction, mesenteric ischaemia, or severe chronic inflammatory bowel disease. In addition, patients had to have norm al function (calculated creatinine clearance ≥50 mL/min and functional contralateral kidney), normal bone marrow and hepatic function (white blood cell count ≥2.5 × 10^9 cells per L, platelet count ≥80 × 10^9 cells per L, and total bilirubin <2 times upper limit of normal); cardiac function less than or equal to New York Heart Association class II; normal 12 lead electrocardiogram; a negative pregnancy test within 3 weeks before the first day of study treatment; adequate birth control measures; no relevant previous abdominal or pelvic	of randomisation in the same centre as surgery. The prescribed dose was 50.4 Gy in 28 once-daily fractions of 1.8 Gy, with five fractions per week during 5.5 weeks.		patients refused radiotherapy, 1 radiotherapy planning not acceptable), 2 did not have radiotherapy and did not have surgery (1 withdrew consent for the study, 1 non-eligible tumour identified by central pathology review) Control: 5 (4%) Reasons: 5 patients did not have surgery (2 distant metastasis, 1 did not meet operability criteria, 1 had problem with anaesthesia, 1 died before surgery) <u>Incomplete outcome data</u>: Intervention: 7 (6%) Reasons not described. Control: 4 (3%) Reasons not described.	<u>Quality of life</u> QLQ-C30 questionnaires at baseline, year 1, and year 5. Compliance was low and data were too sparse to allow any meaningful estimation of treatment differences, thus, results will not be reported. <u>Safety</u> Adverse events: Common Terminology Criteria for Adverse Events (CTCAE) version 4.018. Serious adverse events (not further specified) I: 30 (24%) of 127 C: 13 (10%) of 128 RR = 2.33 (95%CI 1.27 to 4.25) Mortality: I: 1/127 C: 0/128	

	from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Pfizer, Blueprint Medicines, Pierre Fabre, and Sanofi, outside the submitted work. PC reports personal fees from AbbVie and AstraZeneca, outside the submitted work. AM reports grants from National Health Service (NHS) funding to the National Institute for Health Research Biomedical Research Centre for Cancer at The Royal Marsden Hospital and The Institute of Cancer Research, during the conduct of the study. JYB reports grants from European Clinical Trials in Rare Sarcomas (EUROSARC), Lyon Integrative Cancer Research Program (LYRICAN), the European Network for Rare Adult Solid Cancers (EURACAN), NetSarc+, and Intersarc, during the conduct of the study. APDT reports personal fees from Roche, PharmaMar, and Bayer, outside the submitted work. All	radiation; no co-existing malignancy within the last 5 years, except for adequately treated basal cell carcinoma of the skin or carcinoma in the cervix; and no psychological, familial, sociological, or geographical conditions that could interfere with compliance with the study protocol. <u>Exclusion criteria</u>: Patients were ineligible if a macroscopically incomplete (R2) surgery was anticipated on the prerandomisation CT scan and if the tumour was one of the following histological subtypes: gastrointestinal stromal tumour, rhabdomyosarcoma, primitive neuroectodermal tumour or other small round blue cell sarcoma, osteosarcoma, chondrosarcoma, aggressive fibromatosis, or sarcomatoid or metastatic carcinoma. <u>N total at baseline</u>: Intervention: 133 Control: 133 <u>Important prognostic factors</u>:					

	other authors declare no competing interests.	*age median (IQR)* *I: 61 (52-68)* *C: 61 (53-67)* *Sex:* *I: 53% M* *C: 50% M* *WHO performance status:* *I: 0: 83%, 1: 17%, 2: <1%* *C: 0: 75%, 1: 25%, 2: 0%* Groups comparable at baseline.					
Yang, 1998 (long term follow-up: Beane, 2014)	Type of study: RCT Setting and country: Setting not reported, Bethesda, USA Funding and conflicts of interest: Not reported.	<u>Inclusion criteria</u>: Patients with extremity soft tissue tumors of high or low grade: *the study included both high and low grade tumors, data is only extracted for the subgroup of patients with low-grade tumors.* <u>Exclusion criteria</u>: Patients with evidence of metastatic disease, a history of a second malignancy, or contraindications to receiving doxorubicin, cyclophosphamide, or XRT were excluded. <u>N total at baseline</u>: Intervention: 26 Control: 24 <u>Important prognostic factors</u>:	Intervention group: surgery and adjuvant radiotherapy (XRT). Surgery: Patients who presented with recent excision of their primary tumors were widely re-excised at the NCI, unless clear documentation was available to confirm the adequacy of the previous surgery. As a minimum, surgery had to result in the removal of all gross disease. In patients with a prior operation, definitive surgery was planned to entirely encompass the previous surgery, including all biopsy and drain sites. Wherever possible, a margin of 1 to 2 cm of normal tissue	Control group: surgery only. Surgery: similar to intervention group, see description.	<u>Length of follow-up</u>: Yang, 1998: All patients were followed up by clinical assessment and chest radiograph every 2 to 3 months for 2 years, 3 to 4 months for 2 more years, and 6 to 12 months at 4 years and beyond. Beane 2014: a 20-year follow-up (update). <u>Loss-to-follow-up</u>: Yang, 1998: There was one protocol violation in which a patient refused XRT after randomization. She	<u>Overall survival</u> There have been four deaths from metastatic disease among patients with low-grade tumors (two in each treatment arm), with only one of these patients having a local recurrence. Overall survival (Beane 2014): proportion surviving reported graphically until 30 years after randomization, P2 = 0.14. <u>Progression-free survival</u> Not reported. <u>Local recurrence</u> Local recurrence- free survival is reported graphically for a follow-up period of 12 years. With a median follow-up of 9.9 years (range 1.4 to 12.4 years), eight patients randomized to not receive XRT have locally recurred,	Author's conclusion: In this prospective randomized trial, adjuvant postoperative external-beam radiotherapy was shown to result in a statistically significant reduction in LRs in patients with either high-grade or low-grade extremity tumors. Overall survival and nonlocal recurrences were nearly identical for patients receiving or not receiving radiation. (…) With different strategies yielding similar overall survival

		Age ± SD: *I: not reported* *C: not reported* *Sex:* *I: 58% M* *C: 71% M* Groups comparable at baseline: Demographic characteristics in these two patient populations were evenly distributed.	or an uninvolved fascial boundary was maintained around the tumor specimen. This standard was compromised only if a limited positive (or close) surgical margin would spare the patient the disabilities resulting from resection of major nerves, vessels, or weight-bearing bone. Resections included periosteum or vessel adventitium in continuity where necessary. Patients with gross residual tumor or multiple, widely positive margins following maximum LSS were offered amputation and not included in the study. Adjuvant XRT: randomized within 4 months of definitive resection. Radiation consisted of 4,500 cGy to a wide field followed by an 1,800 cGy boost to the tumor bed (as defined by perimeter surgical clips). Care was taken to avoid circumferential limb irradiation and unnecessary irradiation of joints and tissues not		is included in all analyses according to randomization. Beane, 2014: Since the original publication 55 patients have died (39 %), 19 (13 %) have been lost to follow-up, and 76 (48 %) confirmed living. Of the patients confirmed living, 54 (71 %) completed telephone interviews. A total of 22 patients (29 %) did not complete the questionnaire because they were unwilling to participate or were unable to be contacted by telephone and thus excluded.	and one treated with XRT has locally recurred. <u>Quality of life</u> Functional Living Index-Cancer (FLIC) (154 = best score): Baseline: 114/112 6 months: 118/125 12 months: 129/127 24 months: 125/130 36 months: 131/127 Independence in activities of daily living, modified Erdman scale: No scores reported, only described as no significant differences between patients in the two treatment arms. <u>Safety</u> Beane, 2014: wound complications, number of patients that required wound care or subsequent major surgical interventions: I: 8/30 patients (27%; 95% CI 12 to 46%) C: 5/24 patients (20%; 95% CI 7 to 42%) .	rates, recommendations for the use of XRT may rest primarily on quality-of-life issues and individual patient risk factors for LR. Although this study had too few local failures to identify risk factors for LR (other than lack of XRT), previous studies have suggested that previous recurrence and surgical margins have the greatest impact on local recurrence. Author's conclusion Beane, 2014: In summary, the initial results of this study demonstrated that adjuvant EBRT for extremity STS improves local control without a statistically significant improvement in overall survival. Although it is possible an OS benefit exists but was not detected

			at risk, through the use of filters, compensatory wedges, and electrons. One hundred eighty cGy fractions were given 5 days a week for a total of 6 to 7 weeks of therapy. Therapy was delayed for marked cutaneous reactions or wound complications.				due to limited power, this has remained true on long-term follow-up. Our recommendation has been that adjuvant EBRT be reserved for those with significant risk of local recurrence to avoid multiple surgeries and limb loss from such preventable recurrences. In our study some late limb-loss events occurred in patients who had undergone EBRT, and we maintain that its use for patients at low risk of recurrence should be selective.

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure**

	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	**Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	**LOW** **Some concerns** **HIGH**
Bonvalot, 2020	Definitely yes Reason: Patients were randomly assigned (1:1) centrally, at the headquarters of the European Organisation for Research and Treatment of Cancer (EORTC), using an interactive web response system, to receive either en-bloc curative-intent surgery alone or preoperative radiotherapy followed by en-bloc curative-intent surgery. Randomisation was stratified by hospital and WHO performance status (0–1 vs 2) using a	Definitely yes Reason: Central assignment at the headquarters.	Definitely no Reason: open-label study. No masking of treatment assignments was possible because of the differences in treatment.	Probably yes Reason: Loss to follow-up was relatively infrequent and similar across groups. All randomly assigned patients were included in the intention-to-treat analysis.	Probably yes Reason: Relevant outcomes were reported. Quality of life data was not reported, but it was explained why (Compliance was low and data were too sparse to allow any meaningful estimation of treatment differences, thus, results will not be reported.)	Probably yes Reason: No other problems noted.	LOW

	minimisation algorithm, and was not balanced by histological subtype.						
Yang, 1998 (Beane, 2014)	Definitely yes Reason: A fixed block randomization with stratification for primary versus recurrent tumors, grade 1 versus aggressive benign lesions and positive versus negative surgical margins was used.	No information about allocation concealment.	Definitely no Reason: blinding not possible due to the type of intervention treatment (radiotherapy)	Probably yes Reason: infrequent: There was one protocol violation in which a patient refused XRT after randomization. She is included in all analyses according to randomization.	Probably yes Reason: all relevant outcomes from methods section are reported (no protocol available)	Probably yes Reason: No other problems noted, but no information on funding and possible conflicts of interest.	Some concerns

Table of excluded studies

Reference	Reason for exclusion
Abouarab MH, Salem IL, Degheidy MM, Henn D, Hirche C, Eweida A, Uhl M, Kneser U, Kremer T. Therapeutic options and postoperative wound complications after extremity soft tissue sarcoma resection and postoperative external beam radiotherapy. Int Wound J. 2018 Feb;15(1):148-158. doi: 10.1111/iwj.12851. Epub 2017 Dec 5. PMID: 29205902; PMCID: PMC7950197.	wrong intervention
Adishesh M, Terefenko H, Taylor S, Decruze B, Lord R, Herod J. Adjuvant treatment after hysterectomy for uterine leiomyosarcoma. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD011527. DOI: 10.1002/14651858.CD011527.	wrong design: protocol
Albertsmeier M, Rauch A, Roeder F, Hasenhütl S, Pratschke S, Kirschneck M, Gronchi A, Jebsen NL, Cassier PA, Sargos P, Belka C, Lindner LH, Werner J, Angele MK. External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2018 Mar;25(3):754-767. doi: 10.1245/s10434-017-6081-2. Epub 2017 Sep 11. PMID: 28895107.	SR includes only 1 RCT, included separately
Bedi M, Ethun CG, Charlson J, Tran TB, Poultsides G, Grignol V, Howard JH, Tseng J, Roggin KK, Chouliaras K, Votanopoulos K, Cullinan D, Fields RC, Cardona K, King DM. Is a Nomogram Able to Predict Postoperative Wound Complications in Localized Soft-tissue Sarcomas of the Extremity? Clin Orthop Relat Res. 2020 Mar;478(3):550-559. doi: 10.1097/CORR.0000000000000959. PMID: 32168066; PMCID: PMC7145071.	wrong study design: no RCT
Bedi M, Singh R, Charlson JA, Kelly T, Johnstone C, Wooldridge A, Hackbarth DA, Moore N, Neilson JC, King DM. Is 5 the New 25? Long-Term Oncologic Outcomes From a Phase II, Prospective, 5-Fraction Preoperative Radiation Therapy Trial in Patients With Localized Soft Tissue Sarcoma. Adv Radiat Oncol. 2022 Jan 25;7(3):100850. doi: 10.1016/j.adro.2021.100850. PMID: 35647402; PMCID: PMC9133395.	no comparison between RT vs no RT (concerns the effect of RT in 5 fractions every other day)
Bonvalot S, Rutkowski PL, Thariat J, Carrère S, Ducassou A, Sunyach MP, Agoston P, Hong AM, Mervoyer A, Rastrelli M, Moreno V, Li RK, Tiangco BJ, Herráez AC, Gronchi A, Sy-Ortin T, Hohenberger P, de Baère T, Cesne AL, Helfre S, Saada-Bouzid E, Anghel RM, Kantor G, Montero A, Loong HH, Vergés R, Kacso G, Austen L, Servois VF, Wardelmann E, Dimitriu M, Said P, Lazar AJ, Bovée JVMG, Péchoux CL, Pápai Z. Final Safety and Health-Related Quality of LIfe Results of the Phase 2/3 Act.In.Sarc Study With Preoperative NBTXR3 Plus Radiation Therapy Versus Radiation Therapy in Locally Advanced Soft-Tissue Sarcoma. Int J Radiat Oncol Biol Phys. 2022 Nov 1;114(3):422-432. doi: 10.1016/j.ijrobp.2022.07.001. Epub 2022 Jul 16. PMID: 35850363.	wrong comparison (NBTXR+RT vs RT)
Boughzala-Bennadji R, Stoeckle E, Le Péchoux C, Méeus P, Honoré C, Attal J, Duffaud F, De Pinieux G, Bompas E, Thariat J, Leroux A, Bertucci F, Isambert N, Delcambre C, Blay JY, Sunyach MP, Coindre JM, Sargos P, Penel N, Bonvalot S. Localized Myxofibrosarcomas: Roles of Surgical	wrong study design: no RCT

Margins and Adjuvant Radiation Therapy. Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):399-406. doi: 10.1016/j.ijrobp.2018.05.055. Epub 2018 Jun 2. PMID: 30191871.	
Chang X, Li Y, Xue X, Zhou H, Hou L. The current management of alveolar soft part sarcomas. Medicine (Baltimore). 2021 Aug 6;100(31):e26805. doi: 10.1097/MD.0000000000026805. PMID: 34397835; PMCID: PMC8341245.	wrong study design: no systematic review
Chen YT, Tu WT, Lee WR, Huang YC. The efficacy of adjuvant radiotherapy in dermatofibrosarcoma protuberans: a systemic review and meta-analysis. J Eur Acad Dermatol Venereol. 2016 Jul;30(7):1107-14. doi: 10.1111/jdv.13601. Epub 2016 Feb 16. PMID: 26879523.	wrong study design: no RCT
Cheng H, Miura JT, Lalehzari M, Rajeev R, Donahue AE, Bedi M, Gamblin TC, Turaga KK, Johnston FM. Neoadjuvant radiotherapy for retroperitoneal sarcoma: A systematic review. J Surg Oncol. 2016 May;113(6):628-34. doi: 10.1002/jso.24221. Epub 2016 Mar 16. PMID: 26990903.	wrong comparison
Correa R, Gómez-Millán J, Lobato M, Fernández A, Ordoñez R, Castro C, Lupiañez Y, Medina JA. Radiotherapy in soft-tissue sarcoma of the extremities. Clin Transl Oncol. 2018 Sep;20(9):1127-1135. doi: 10.1007/s12094-018-1848-x. Epub 2018 Feb 23. PMID: 29476322.	wrong study aim: describe current standard of treatment
De Amorim Bernstein K, Delaney TF. Role of radiation therapy for non-extremity soft tissue sarcomas. J Surg Oncol. 2015 Apr;111(5):604-14. doi: 10.1002/jso.23863. Epub 2014 Dec 29. PMID: 25556548.	no systematic search
Diamantis A, Baloyiannis I, Magouliotis DE, Tolia M, Symeonidis D, Bompou E, Polymeneas G, Tepetes K. Perioperative radiotherapy versus surgery alone for retroperitoneal sarcomas: a systematic review and meta-analysis. Radiol Oncol. 2020 Feb 29;54(1):14-21. doi: 10.2478/raon-2020-0012. PMID: 32114526; PMCID: PMC7087419.	SR does not include RCTs
Dunst J. Prä- oder postoperative Strahlentherapie bei retroperitonealen Sarkomen unverzichtbar [Pre- or postoperative radiotherapy essential for the treatment of retroperitoneal sarcomas]. Strahlenther Onkol. 2016 Nov;192(11):820-822. German. doi: 10.1007/s00066-016-1042-4. PMID: 27596218.	wrong language
Gervais MK, Callegaro D, Gronchi A. The evolution of adjuvant/neoadjuvant trials for resectable localized sarcoma. J Surg Oncol. 2022 Jan;125(1):17-27. doi: 10.1002/jso.26745. PMID: 34897708.	not a systematic review
Guadagnolo BA, Bassett RL, Mitra D, Farooqi A, Hempel C, Dorber C, Willis T, Wang WL, Ratan R, Somaiah N, Benjamin RS, Torres KE, Hunt KK, Scally CP, Keung EZ, Satcher RL, Bird JE, Lin PP, Moon BS, Lewis VO, Roland CL, Bishop AJ. Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2022 Dec;23(12):1547-1557. doi: 10.1016/S1470-2045(22)00638-6. Epub 2022 Nov 4. PMID: 36343656; PMCID: PMC9817485.	no comparison (concerns the safety of a shorter regimen)

Haas RL, Miah AB, LePechoux C, DeLaney TF, Baldini EH, Alektiar K, O'Sullivan B. Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies. Radiother Oncol. 2016 Apr;119(1):14-21. doi: 10.1016/j.radonc.2015.12.002. Epub 2015 Dec 21. PMID: 26718153; PMCID: PMC5506844.	wrong study design: critical review
Hoefkens F, Dehandschutter C, Somville J, Meijnders P, Van Gestel D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. Radiat Oncol. 2016 Oct 12;11(1):136. doi: 10.1186/s13014-016-0668-9. PMID: 27733179; PMCID: PMC5062836.	wrong study design: no systematic review
Kannan S, Chong HH, Chew B, Ferguson JD, Galloway E, McCulloch T, Rankin KS, Ashford RU. Leiomyosarcoma in the extremities and trunk wall: systematic review and meta-analysis of the oncological outcomes. World J Surg Oncol. 2022 Apr 18;20(1):124. doi: 10.1186/s12957-022-02584-4. PMID: 35436892; PMCID: PMC9014567.	wrong research aim (prognostic impact of markers)
Kelly KJ, Yoon SS, Kuk D, Qin LX, Dukleska K, Chang KK, Chen YL, Delaney TF, Brennan MF, Singer S. Comparison of Perioperative Radiation Therapy and Surgery Versus Surgery Alone in 204 Patients With Primary Retroperitoneal Sarcoma: A Retrospective 2-Institution Study. Ann Surg. 2015 Jul;262(1):156-62. doi: 10.1097/SLA.0000000000001063. PMID: 26061213; PMCID: PMC4465112.	wrong study design: no RCT
Kungwengwe G, Clancy R, Vass J, Slade R, Sandhar S, Dobbs TD, Bragg TWH. Preoperative versus Post-operative Radiotherapy for Extremity Soft tissue Sarcoma: a Systematic Review and Meta-analysis of Long-term Survival. J Plast Reconstr Aesthet Surg. 2021 Oct;74(10):2443-2457. doi: 10.1016/j.bjps.2021.05.043. Epub 2021 Jun 9. PMID: 34266806.	SR includes only 1 RCT, included separately
Lane WO, Cramer CK, Nussbaum DP, Speicher PJ, Gulack BC, Czito BG, Kirsch DG, Tyler DS, Blazer DG 3rd. Analysis of perioperative radiation therapy in the surgical treatment of primary and recurrent retroperitoneal sarcoma. J Surg Oncol. 2015 Sep;112(4):352-8. doi: 10.1002/jso.23996. Epub 2015 Aug 4. PMID: 26238282.	wrong study design: no RCT
Lansu J, Bovée JVMG, Braam P, van Boven H, Flucke U, Bonenkamp JJ, Miah AB, Zaidi SH, Thway K, Bruland ØS, Baldini EH, Jebsen NL, Scholten AN, van den Ende PLA, Krol ADG, Ubbels JF, van der Hage JA, van Werkhoven E, Klomp HM, van der Graaf WTA, van Coevorden F, Schrage Y, van Houdt WJ, Haas RL. Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma: A Nonrandomized Controlled Trial. JAMA Oncol. 2021 Jan 1;7(1):e205865. doi: 10.1001/jamaoncol.2020.5865. Epub 2021 Jan 21. PMID: 33180100; PMCID: PMC7662477.	wrong comparison (concerns dose reduction instead of RT vs no RT)
Lansu J, Braam PM, van Werkhoven E, Scholten AN, Schrage Y, van Houdt WJ, van Langevelde K, Haas RL. A moderate dose of preoperative radiotherapy may improve resectability in myxoid liposarcoma. Eur J Surg Oncol. 2021 Oct;47(10):2633-2639. doi: 10.1016/j.ejso.2021.06.020. Epub 2021 Jun 23. PMID: 34233858.	no comparison between RT vs no RT (concerns the effect of a moderate radiotherapy dose on resectability)

Lazarev S, McGee H, Moshier E, Ru M, Demicco EG, Gupta V. Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: Nationwide patterns of care and trends in utilization. Pract Radiat Oncol. 2017 Nov-Dec;7(6):e507-e516. doi: 10.1016/j.prro.2017.04.010. Epub 2017 Apr 18. PMID: 28551391; PMCID: PMC6004789.	wrong study design: no RCT
Levy A, Honoré C, Dumont S, Bourdais R, Cavalcanti A, Faron M, Ngo C, Haddag-Miliani L, Le Cesne A, Mir O, Le Péchoux C. Radiothérapie préopératoire versus postopératoire dans les sarcomes des tissus mous : état des lieux et perspectives [Preoperative versus postoperative radiotherapy in soft tissue sarcomas: State of the art and perspectives]. Bull Cancer. 2021 Sep;108(9):868-876. French. doi: 10.1016/j.bulcan.2021.03.012. Epub 2021 Jul 8. PMID: 34246458.	wrong language
Li X, Dong R, Xiao M, Min L, Luo C. Neoadjuvant radiotherapy for resectable retroperitoneal sarcoma: a meta-analysis. Radiat Oncol. 2022 Dec 28;17(1):215. doi: 10.1186/s13014-022-02159-3. PMID: 36578082; PMCID: PMC9795731.	SR includes only 1 RCT, included separately
Li X, Wu T, Xiao M, Wu S, Min L, Luo C. Adjuvant therapy for retroperitoneal sarcoma: a meta-analysis. Radiat Oncol. 2021 Oct 7;16(1):196. doi: 10.1186/s13014-021-01774-w. PMID: 34620197; PMCID: PMC8496039.	SR does not include RCTs
Mahmoudi H, Arefpour A, Jamshidi K, Fadavi P, Mirzaei A. Comparison of preoperative and postoperative radiation therapy for extremity soft-tissue sarcoma: a randomized clinical trial. Current Orthopaedic Practice. 2021; 32 (5): 488-494. doi: 10.1097/BCO.0000000000001028.	Wrong comparison (included for other RT module)
Müller DA, Beltrami G, Scoccianti G, Frenos F, Capanna R. Combining limb-sparing surgery with radiation therapy in high-grade soft tissue sarcoma of extremities - Is it effective? Eur J Surg Oncol. 2016 Jul;42(7):1057-63. doi: 10.1016/j.ejso.2016.02.004. Epub 2016 Feb 12. PMID: 26924784.	wrong study design: no RCT
Neugebauer J, Blum P, Keiler A, Süß M, Neubauer M, Moser L, Dammerer D. Brachytherapy in the Treatment of Soft-Tissue Sarcomas of the Extremities-A Current Concept and Systematic Review of the Literature. Cancers (Basel). 2023 Feb 10;15(4):1133. doi: 10.3390/cancers15041133. PMID: 36831476; PMCID: PMC9954233.	wrong intervention, only qualitative analysis
Nussbaum DP, Rushing CN, Lane WO, Cardona DM, Kirsch DG, Peterson BL, Blazer DG 3rd. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol. 2016 Jul;17(7):966-975. doi: 10.1016/S1470-2045(16)30050-X. Epub 2016 May 17. PMID: 27210906.	wrong study design: no RCT
Qu X, Lubitz CC, Rickard J, Bergeron SG, Wasif N. A Meta-Analysis of the Association Between Radiation Therapy and Survival for Surgically Resected Soft-Tissue Sarcoma. Am J Clin Oncol. 2018 Apr;41(4):348-356. doi: 10.1097/COC.0000000000000274. PMID: 26886948.	SR only includes 1 relevant RCT, included separately
Ramey SJ, Yechieli R, Zhao W, Kodiyan J, Asher D, Chinea FM, Patel V, Reis IM, Wang L, Wilky BA, Subhawong T,	wrong study design: no RCT

Trent JC 2nd. Limb-sparing surgery plus radiotherapy results in superior survival: an analysis of patients with high-grade, extremity soft-tissue sarcoma from the NCDB and SEER. Cancer Med. 2018 Sep;7(9):4228-4239. doi: 10.1002/cam4.1625. Epub 2018 Jul 20. PMID: 30030882; PMCID: PMC6144142.	
van Praag VM, Rueten-Budde AJ, Jeys LM, Laitinen MK, Pollock R, Aston W, van der Hage JA, Dijkstra PDS, Ferguson PC, Griffin AM, Willeumier JJ, Wunder JS, van de Sande MAJ, Fiocco M. A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: Personalised sarcoma care (PERSARC). Eur J Cancer. 2017 Sep;83:313-323. doi: 10.1016/j.ejca.2017.06.032. Epub 2017 Aug 8. PMID: 28797949.	wrong study design: no RCT
Wang D, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, Petersen IA, DeLaney TF, Freeman CR, Finkelstein SE, Hitchcock YJ, Bedi M, Singh AK, Dundas G, Kirsch DG. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol. 2015 Jul 10;33(20):2231-8. doi: 10.1200/JCO.2014.58.5828. Epub 2015 Feb 9. PMID: 25667281; PMCID: PMC4486342.	wrong study design: no RCT
Willeumier JJ, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, Dijkstra PD, Ferguson PC, Griffin AM, Wunder JS, Fiocco M, van de Sande MA. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. BMJ Open. 2017 Feb 14;7(2):e012930. doi: 10.1136/bmjopen-2016-012930. PMID: 28196946; PMCID: PMC5318556.	wrong study design: no RCT
Yang X, Zhang L, Yang X, Yu W, Fu J. Oncologic outcomes of pre- versus post-operative radiation in Resectable soft tissue sarcoma: a systematic review and meta-analysis. Radiat Oncol. 2020 Jun 23;15(1):158. doi: 10.1186/s13014-020-01600-9. PMID: 32576267; PMCID: PMC7310344.	SR includes only 1 RCT, included separately

Zoekverantwoording

Database(s): Ovid/Medline, Embase	Datum: 15-5-2023, 23-6-2023
Periode: 2000-	Talen: nvt

5 ***Zoekopbrengst***

Vanaf 2015 23-6-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs			211
RCTs			488
Observationele studies			
Overig			
Totaal			699
15-5-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	275	186	312
RCTs	661	627	1002
Observationele studies			

Overig			
Totaal			1314

Zoekstrategie

Embase

No.	Query	Results
#22	#5 AND #13 AND #21 artikel Gronchi niet gevonden	6
#21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 sleutelartikelen	7
#20	'late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma'	1
#19	'preoperative versus postoperative radiotherapy in soft-tissue sarcoma' AND 2011 AND sampath	1
#18	'individualizing the use/non-use of radiation therapy (rt) in soft tissue sarcoma (sts): when abstention is better than care'	1
#17	'complications of combined modality treatment of primary lower extremity soft tissue sarcomas'	1
#16	'preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs'	1
#15	'efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity'	1
#14	'adequate local control in high-risk soft tissue sarcoma of the extremity treated with surgery alone at a reference centre'	1
#13	#10 OR #11 OR #12	3003
#12	#5 AND (#8 OR #9) NOT #10 NOT #11	2067
#11	#5 AND #7 NOT #10 Clinical trials, RCTs	661
#10	#5 AND #6 SR	275
#9	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational	14073538

	study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3302394
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#5	#4 AND [2000-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	9564
#4	#1 AND #2 AND #3	15529
#3	'surgery'/exp/mj OR 'surgical patient'/exp/mj OR 'surgical risk'/exp OR 'perioperative period'/exp OR surgic*:ti,ab,kw OR surger*:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR presurg*:ti,ab,kw OR preoperati*:ti,ab,kw OR perisurg*:ti,ab,kw OR perioperati*:ti,ab,kw OR	5718949

	postsurg*:ti,ab,kw OR postoperati*:ti,ab,kw OR laparoscop*:ti,ab,kw OR intraoperati*:ti,ab,kw	
#2	'radiotherapy'/exp/mj OR 'bioradiant therapy':ti,ab,kw OR 'bucky ray':ti,ab,kw OR 'bucky therapy':ti,ab,kw OR 'radio therapy':ti,ab,kw OR 'radio treatment':ti,ab,kw OR 'radiohypophysectomy':ti,ab,kw OR 'radiotherapy':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'roentgen treatment':ti,ab,kw OR 'rontgen therapy':ti,ab,kw OR 'therapeutic radiology':ti,ab,kw OR 'x radiotherapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw OR 'x-ray therapy':ti,ab,kw OR irradiati*:ti,ab,kw OR radiati*:ti,ab,kw	1072427
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)	106090

Ovid/Medline

#	Searches	Results
14	11 or 12 or 13	2479
13	((8 or 9) and 10) not 11 not 12	1666
12	(7 and 10) not 11 Clinical trials, RCT	627
11	6 and 10 SR	186
10	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	4696
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient*	5422320

	or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4436464
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2587457
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	667693
5	limit 4 to yr="2000 -Current"	4853
4	1 and 2 and 3	6598
3	exp Radiotherapy/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,ab,kf.	811912
2	exp Surgical Procedures, Operative/ or exp Specialties, Surgical/ or su.fs. or exp Perioperative Period/ or surgic*.ti,ab,kf. or surger*.ti,ab,kf. or operation*.ti,ab,kf. or operative.ti,ab,kf. or presurg*.ti,ab,kf. or	5516780

	preoperati*.ti,ab,kf. or perisurg*.ti,ab,kf. or perioperati*.ti,ab,kf. or postsurg*.ti,ab,kf. or postoperati*.ti,ab,kf. or laparoscop*.ti,ab,kf.	
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 sarcoma*).ti,ab,kf.	54351

Module 4.3 – Volgorde chirurgie en radiotherapie

Search and select

A systematic review of the literature was performed to answer the following question:
What is the optimal sequence of surgery and radiotherapy in patients with soft tissue sarcoma?

P: Patient with soft tissue tumor
I: Resection followed by radiotherapy
C: Radiotherapy followed by resection
O: Local recurrence, overall survival, progression free survival, quality of life, safety

Relevant outcome measures

The guideline development group considered local recurrence as a critical outcome measure for decision making; and overall survival, progression free survival, quality of life, safety (adverse events and wound problems/wound healing) as an important outcome measure for decision making.

The working group defined the minimal clinical important differences for the outcomes overall survival, progression free survival, local recurrence, quality of Life, safety (adverse events and wound problems/healing) based on the 'PASKWIL criteria adjuvante behandeling' (NVMO, 2023), and for the other outcomes based on relevant literature:

- Overall survival: > 3 years median follow-up; >5%; >3% and HR < 0.70.
- Progression free survival: HR < 0.60.
- Local recurrence: 25%.
- Safety (adverse events and wound problems/healing): adverse events: lethal <5%, acute or severe <25%)
- Quality of life: The minimum important difference (MID) has been estimated to be a difference of 0.08 or more points for the EQ-5D utility index and seven or more points for the EQ-5D VAS (Pickard, 2007). For quality of life measured with the EORTC QLQ-C30, a difference of 10 points was considered as a clinical important difference (Fiteni, 2016).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 15 May 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search was combined with the search for module 8 ((neo)adjuvant radiotherapy) and resulted in 699 hits. Studies were selected based on the following criteria:

- study design: randomized controlled trial or systematic review.
- adult patients with soft tissue sarcoma who underwent preoperative radiotherapy and surgery vs surgery and postoperative radiotherapy).
- describing at least one of the relevant outcomes specified in the PICO.

Initially, 39 studies were selected for both modules based on title and abstract screening. After reading the full text, 38 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included for the current module.
Subsequently, the references of the ESMO EURACAN GENTURIS Clinical Practice Guidelines (2021) were searched for additional relevant studies published before 2015. As a result, one additional study was included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Mahmoudi (2021) conducted a randomized clinical trial to compare the rate and severity of complications as well as oncologic outcomes of preoperative and postoperative radiotherapy in patients with pathology-confirmed localized extremity soft-tissue sarcoma. Patients were excluded if they were below 18 years, were pregnant, had remote metastasis, had an ECOP ECOG PS>2, or had a soft-tissue disorder. Eighty eligible patients were included, and were allocated to either the preoperative (n=40) or postoperative (n=40) radiotherapy group. Patients in the intervention group (postoperative radiotherapy) initially underwent limb-preservation surgery. After surgical wound healing that generally took 3 to 6 weeks, postoperative radiotherapy was applied in two phases. Patients in the control group (preoperative radiotherapy) were referred to the radiation oncologist before surgery and received radiotherapy. Surgery was performed 4 to 6 weeks after completing the radiotherapy. Baseline characteristics did not differ between intervention and control group. The length of the follow-up period was 12 months.

O'Sullivan (2002) conducted a multicenter randomized controlled trial to determine whether scheduling of external beam radiotherapy (preoperative versus postoperative) affected the rate of wound complications. Patients were included when they were in need of combined radiotherapy and surgery, having the diagnosis of soft-tissue sarcoma by an approved reference pathologist, having first or recurrent presentations, being over 15 years, having written informed consent, having a chest CT, and having had an CT or MRI. Patients were stratified according to tumor size (=< 10 cm or > 10 cm). A total of 94 patients were randomly allocated to preoperative radiotherapy (50 Gy in 25 fractions) group, and 96 patients were allocated to postoperative radiotherapy (66 Gy in 33 fractions) group. Surgery and radiotherapy were done 3-6 weeks apart in both groups. The length of the follow-up period was until 120 days of surgery. Baseline characteristics did not differ between intervention and control group.

Results

Local recurrence

Mahmoudi (2021) reported local recurrence. Solely one patient in the intervention group (2.5%) reported local recurrence, in the control group no patient (0%) reported local recurrence (Risk Difference (RD) 0.03; 95% CI -0.04 to 0.09).

O'Sullivan (2002) reported local recurrence solely using Kaplan-Meier curves. In the intervention group, 91.8% was event-free of local recurrence, this was respectively 94% in the control group.

Overall survival

Mahmoudi (2021) reported overall survival. In the intervention group (postoperative radiotherapy) (n=40), an overall survival of 35 (87.5%) was reported at one-year follow-up. In the control group (preoperative radiotherapy) (n=40), an overall survival of 37 (92.5%) patients was reported at one-year follow-up (Risk Ratio (RR) 0.95; 95% CI 0.81 to 1.10).

O'Sullivan (2002) reported overall survival. In the intervention group (postoperative radiotherapy) (n=96), 68 (72%) of the patients was alive at 3.5 years follow-up. In the control

group (preoperative radiotherapy) (n=94), 78 (85%) of the patients was alive at 3.5 years follow-up (RR 0.85; 95% CI 0.73 to 1.00).

Progression free survival

O'Sullivan (2002) reported progression free survival, solely using Kaplan-Meier plots. It was mentioned textually that progression-free survival did not differ between groups. No other data were provided. **Mahmoudi (2021)** did not report progression free survival.

Quality of life

O'Sullivan (2002) reported quality of life solely textually, stating that '*quality of life, is significantly associated with wound complication after limb conservation management for soft-tissue sarcoma*'. **Mahmoudi (2021)** did not report quality of life.

Safety (adverse events)

Mahmoudi (2021) reported both wound infections and dehiscence, which was assessed by the responsible surgeon during the first postoperative months. In the intervention group (postoperative radiotherapy) (n=40), 1 (2.5%) patient reported wound infections and dehiscence. In the control group (preoperative radiotherapy (n=40), 3 patients (7.5%) reported wound infection and dehiscence (RD -0.05; 95% CI -0.14 to 0.04).

O'Sullivan (2002) reported wound complications up to 4 months after surgery. In the intervention group (postoperative radiotherapy) (n=96), 16 (17%) of the patients reported wound complications. In the control group (preoperative radiotherapy) (n=94), 31 (35%) of the patients reported wound complications (RD -0.16; 95% CI -0.28 to -0.04).

<u>Level of evidence of the literature</u>

The level of evidence for all outcomes under this comparison was based on randomized studies and therefore starts at high.

Local recurrence

The level of evidence regarding the outcome measure **local recurrence** was downgraded by two levels to **low** because of study limitations (risk of bias, -1), OIS was not met (imprecision, -1).

Overall survival

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of study limitations (risk of bias, -1), the OIS was not met (imprecision, -1).

Progression free survival

The level of evidence regarding the outcome measure **progression free survival** was downgraded by two levels to **low** because of study limitations (risk of bias, -1), OIS was not met (imprecision, -1).

Quality of life

As none of the included studies reported quantitative data on **quality of life**, it was not possible to assess the level of evidence.

Safety (adverse events)

The level of evidence regarding the outcome measure **safety (adverse events)** was downgraded by two levels to **low** because of study limitations (risk of bias, -1), confidence interval crossing one threshold for clinical relevance (imprecision, -1).

Conclusions

Low GRADE	Postoperative radiotherapy may result in little to no difference in **local recurrence** when compared with preoperative radiotherapy in patients with soft-tissue sarcoma. *Source*: *Mahmoudi (2021)*

Low GRADE	Postoperative radiotherapy may result in little to no difference in **overall survival** when compared with preoperative radiotherapy in patients with soft-tissue sarcoma. *Source: Mahmoudi (2021); O'Sullivan (2002)*

Low GRADE	Postoperative radiotherapy may result in little to no difference in **progression free survival** when compared with preoperative radiotherapy in patients with soft-tissue sarcoma. *Source: O'Sullivan (2002)*

NO GRADE	No evidence was found regarding the effect of postoperative radiotherapy on **quality of life** when compared with preoperative radiotherapy in patients with soft-tissue sarcoma. *Source: -*

Low GRADE	Postoperative radiotherapy may result in little to no difference in **safety (adverse events)** with regard to wound complications when compared with preoperative radiotherapy in patients with soft-tissue sarcoma. *Source: Mahmoudi (2021); O'Sullivan (2002)*

Kennislacunes

What is the optimal sequence of surgery and radiotherapy in patients with soft tissue tumors?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	Geen nieuwe behandelvormen	nvt	

					voorgeste ld		

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
1st author, year of publication	Type of study: Setting and country: Funding and conflicts of interest:	Inclusion criteria: Exclusion criteria: N total at baseline: Intervention: Control: Important prognostic factors[2]: *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline?	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available):	
Mahmoudi, 2021	Type of study: RCT	Inclusion criteria: -patients who had pathology-confirmed	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up: 12 months	Outcome measures and effect size (include 95%CI and p-value if available):	Comments:

	Setting and country: Patients referred to the orthopaedic clinic of the authors' hospital from 2017 to 2019 were included (Department of Radiation Oncology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran) Funding and conflicts of interest: Authors declare not conflicts of interest. Funding not reported	localized extremity STS (defined as extending from the medical border of the scapula to the fingers and from the iliac crest to the toes), -age >18 yr, -Eastern Cooperative Oncolgy Group (ECOG) functional status score less than 2. Exclusion criteria: Remote metastasis, -pregnancy, -history of connective tissue disease such as lupus. N total at baseline: 80 Intervention: 40 Control: 40 Important prognostic factors[2]: *For example* *age ± SD (years):* *I (postRT): 48.97 ± 15.03* *C: 45.95 ± 16.87* *Sex (n, %):* *I (postRT): 24 (60%) % M* *C: 27 (67.5%) % M* Groups comparable at baseline? Yes	Patients with extremity soft-tissue sarcoma (STS) postoperative radiotherapy group: patients initially underwent limb-preservation surgery. After surgical wound healing that generally took 3 to 6 wk, postoperative radiotherapy was done by the same radiation oncologist and a mean radiotherapy dose of 60 to 66 Gy in the same Gy per fraction. Postoperative radiotherapy was done in two phases. In the first phase, a volume of 5 cm proximal and distal to the target tissue was radiated. Then, the volume was reduced to 2 cm around the target. A longitudinal strip of skin and subcutaneous tissue were not irradiated unless it reduced the radiotherapy margins around the target to less than 2 cm that was not confined by an intact fascial boundary.	Patients with extremity soft-tissue sarcoma (STS) Preoperative radiotherapy group: patients were referred to the radiation oncologist before the surgery and received a mean radiotherapy dose of 50 grays (Gy) in 2 Gy per fraction to a volume of 4 cm proximal and distal to the gross tumor. Limb preservation surgery was done 4 to 6 wk after completing the radiotherapy.	Loss-to-follow-up: 0 Intervention: 0 N (%) Reasons (describe) Control: 0 N (%) Reasons (describe) Incomplete outcome data: none Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	**Wound complications: wound dehiscence and wound infections:** **Wound dehiscence** **N (%)** I (post RT): 1 (2.5%) C (pre RT): 3 (7.5%) **Wound infections** **N (%)** I (post RT): 1 (2.5%) C (pre RT): 3 (7.5%) **Overall survival one-year follow-up (N,%)** Intervention: 35 (87.5%) Controle: 37 (92.5%) **Local recurrence (N, %)** Intervention: 1 (2.5%) Control: 0 (0%) p-value: 0.99 **Quality of life** Not reported **Progression free survival** Not reported **Safety (adverse events)** Not reported	registered on the Iranian Registry of Clinical Trials under the code of IRCT20180919041070N3 -At a short follow-up interval, preoperative and postoperative radiotherapy resulted in the same oncologic outcome in the extremity STS

<table>
<tr>
<td>O'Sullivan (2002)</td>
<td><u>Type of study:</u>
RCT

<u>Setting and country:</u>
Trial opened in October 1994 and closed in December 1997. Further information not provided. Assumed that hospital first author (Toronto, Canada) is where trial occurred.

<u>Funding and conflicts of interest:</u>
Our work was funded by the National Cancer Institute of Canada. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation , or</td>
<td><u>Inclusion criteria:</u>
-need for combined radiotherapy and surgery,
-diagnosis of soft-tissue sarcoma by an approved reference pathologist, -first or recurrent presentations,
- age > 15 years,
- written informed consent, - Chest CT, - local CT or MRI

<u>Exclusion criteria:</u>
-Previous chemotherapy, - Previous radiotherapy to the local site , - Chemotherapy needed for this soft-tissue sarcoma, -Age <16 years, -Presence of regional or distant metastasis, -Previous or concurrent malignant disease, - Histologies generally treated with chemotherapy (a. Embryonal and alveolar rhabdomyosarcoma, b. Soft-tissue osteosarcoma and Ewings' sarcoma, and c. Primitive neuroectodermal tumour), -Benign histologies (a.</td>
<td><u>Describe intervention (treatment/procedure/test):</u>

Patients whom received external-beam radiotherapy in local management of sarcomas in the soft tissue of limbs.

Surgery and radiotherapy were done 3–6 weeks apart.
Procedure: initially radiated a volume of 5 cm proximal and distal to the tissues at risk (phase I) with 50 Gy given in 2 Gy fractions. We then reduced the volume to 2 cm around the target (phase II), as required by protocol. All patients were
to have phase II treatment (16–20 Gy)</td>
<td><u>Describe control (treatment/procedure/test):</u>

Patients whom received external-beam radiotherapy in local management of sarcomas in the soft tissue of limbs.

Surgery and radiotherapy were done 3–6 weeks apart. Procedure: initially radiated a volume of 5 cm proximal and distal to the tissues at risk (phase I) with 50 Gy given in 2 Gy fractions. We then reduced the volume to 2 cm around the target (phase II), as required by protocol. Patients only had a phase II treatment (16–20 Gy) if pathological assessment showed tumour cells at the resection margin. Phase II was not given until after the wound had healed. We left a longitudinal strip of skin and subcutaneous tissue of a limb untreated for at least half of the course, unless it reduced the radiotherapy margin around the target region to less than 2 cm at any point that was not confined by an intact fascial boundary. Planning, dosimetry, and dose prescription were done in accordance with International Commission</td>
<td><u>Length of follow-up:</u>
Median follow-up 3.3 years (range (0.27-5.6)

<u>Loss-to-follow-up:</u>
<u>Intervention:</u>
<u>N (%)</u> 2
<u>Reasons (describe)</u> 1 had metastases at randomisation , 1 had lung cancer at randomisation

<u>Control: 2</u>
<u>N (%)</u>
<u>Reasons (describe)</u> 1 withdrew consent and the other did not have sarcoma (incorrect pathology assessment)

<u>Incomplete outcome data:</u>
<u>Intervention:</u>
3
<u>N (%)</u>
<u>Reasons (describe)</u> did not receive postoperative</td>
<td><u>Outcome measures and effect size (include 95%CI and p-value if available):</u>

Presence or absence of a major wound complication
<table><tr><th></th><th>intervention</th><th>Control</th></tr><tr><td>yes</td><td>16 (17%)</td><td>31 (35%)</td></tr><tr><td>No</td><td>78 (83%)</td><td>57 (65%)</td></tr></table>
Progression-free survival
<table><tr><td>Intervention</td><td>Control</td><td>p-value</td></tr><tr><td>70%</td><td>68%</td><td>P=0.8349</td></tr></table>Progression-free survival did not differ between groups; not quantified, solely figures (using Kaplan-meier plots) were presented.. Calculations made using https://apps.automeris.io/wpd/

Local recurrence: proportion event-free
<table><tr><td>Intervention</td><td>Control</td><td>p-value</td></tr><tr><td>91.8%</td><td>94%</td><td>P=0.7119</td></tr></table>Local recurrence was not quantified, solely figures (using Kaplan-meier plots) were presented.. Calculations made using https://apps.automeris.io/wpd/

Overall survival over 3.5 years follow-up period (N, %)
<table><tr><td></td><td>Intervention</td><td>Control</td><td>P-value</td></tr><tr><td>Alive</td><td>68 (72%)</td><td>78 (85%)</td><td>P=0.0481</td></tr><tr><td>Dead</td><td>26 (28%)</td><td>14 (15%)</td><td></td></tr></table>
Quality of life
Not quantified, solely reported textually
'quality of life,
is significantly associated with wound complication after</td>
<td><u>Comments:</u>

-clinical trial number not reported

-Our results show that the number of severe wound complications is related to timing of external-beam radiotherapy.</td>
</tr>
</table>

	writing of the report. Conflict of interest statement: none declared.	dermatofibrosarcoma protruberans, b. aggressive fibromatosis). <u>N total at baseline:</u> 190 <u>Intervention:</u> 96 <u>Control:</u> 94 <u>Important prognostic factors[2]:</u> <u>*Tumour size (N, %)*</u> <u>*=< 10 cm*</u> <u>*I: 63 (67%)*</u> <u>*C (pre): 57 (65%)*</u> <u>*> 10 cm*</u> <u>*I: 31 (33%)*</u> <u>*C (pre): 31 (35%)*</u> <u>*Sex:*</u> <u>*I: 51 (54%) M*</u> <u>*C: 48 (55%) M*</u> <u>Groups comparable at baseline?</u> Yes		on Radiation Units guidelines, and all fractions and fields were given daily. We simulated radiotherapy treatment plans and encouraged immobilisation of limbs and planning with CT. Quality assurance of the phase-I radiotherapy plan was required within 3 days of start of radiotherapy.	boost because of a wound complication that manifested during radiotherapy (one patient), severe skin toxic effects in phase I (one), or an acute cardiac event that delayed sarcoma surgery and the patient received preoperative treatment (one). <u>Control:</u> <u>N (%) 4</u> <u>Reasons (describe)</u> did not undergo the protocol surgery and were not eligible for the primary outcome (wound healing 120 days within surgery	*limb conservation management for soft-tissue sarcoma'*. **Safety (adverse events)** Not reported	

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Mahmoudi, 2021	Definitely yes; <u>Reason:</u> Using a computer-generated random number list in a 1:1 ratio, ensuring the equal number of patients being allocated to each study group.	Probably no; <u>Reason:</u> Randomization done by nursing assistant whom was not involved in the treatment of the patients. Not reported how and whether	Probably no; <u>Reason:</u> Solely reported that outcomes were assessed by the responsible surgeon during the first postoperative months. Not reported however can be assumed that	Definitely yes; <u>Reason:</u> Loss to follow-up was infrequent in intervention and control group.	Definitely yes <u>Reason:</u> All relevant outcomes were reported;	Definitely yes; <u>Reason:</u> Sample size calculation performed: To improve the power of the study, the authors included 40 patients in each group. -Funding not reported	Some concerns of bias

		allocation was concealed	health care providers and patients were not blinded.				
O'Sullivan (2002)	Probably yes; <u>Reason:</u> patients were stratified before randomisation by maximum tumour dimension (=<10 cm or >10 cm). Then, randomisation was done by computer-generated block design issued through a telephone call by which the participating centre confirmed the patient's eligibility. Unknown who performed the randomization (solely stated that '*The people who did the randomisation were not involved in treatment of patients or analysis of the data.')*	Probably no; <u>Reason:</u> An approved local reference pathologist verified the diagnosis before randomisation, and lesions were graded in a subsequent central pathology review. We determined the need for combined surgery and radiotherapy and for additional eligibility and exclusion criteria before randomisation (panel).	Probably no; <u>Reason:</u> Not reported. However, differences in Intervention and control, likely that patients and health care providers were not blinded. As regards to outcomes, for instance judging a wound Complication was done by observations by study investigators (subjective).	Probably yes; <u>Reason:</u> Loss to follow-up occurred in both intervention and control groups, however reasons for loss to-follow-up were specified.	Probably no; <u>Reason:</u> Not all relevant outcomes were reported (quantified) for instance overall QALY (solely mentioned textually) and progression-free survival (solely presented in Kaplan-Meier curves).	Probably no; <u>Reason:</u> No clinical trial number provided	High concerns of bias

Table of excluded studies

Reference	Reason for exclusion
Abouarab MH, Salem IL, Degheidy MM, Henn D, Hirche C, Eweida A, Uhl M, Kneser U, Kremer T. Therapeutic options and postoperative wound complications after extremity soft tissue sarcoma resection and postoperative external beam radiotherapy. Int Wound J. 2018 Feb;15(1):148-158. doi: 10.1111/iwj.12851. Epub 2017 Dec 5. PMID: 29205902; PMCID: PMC7950197.	wrong intervention
Adishesh M, Terefenko H, Taylor S, Decruze B, Lord R, Herod J. Adjuvant treatment after hysterectomy for uterine leiomyosarcoma. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD011527. DOI: 10.1002/14651858.CD011527.	wrong design: protocol
Albertsmeier M, Rauch A, Roeder F, Hasenhütl S, Pratschke S, Kirschneck M, Gronchi A, Jebsen NL, Cassier PA, Sargos P, Belka C, Lindner LH, Werner J, Angele MK. External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2018 Mar;25(3):754-767. doi: 10.1245/s10434-017-6081-2. Epub 2017 Sep 11. PMID: 28895107.	SR includes only 1 RCT, included separately
Bedi M, Ethun CG, Charlson J, Tran TB, Poultsides G, Grignol V, Howard JH, Tseng J, Roggin KK, Chouliaras K, Votanopoulos K, Cullinan D, Fields RC, Cardona K, King DM. Is a Nomogram Able to Predict Postoperative Wound Complications in Localized Soft-tissue Sarcomas of the Extremity? Clin Orthop Relat Res. 2020 Mar;478(3):550-559. doi: 10.1097/CORR.0000000000000959. PMID: 32168066; PMCID: PMC7145071.	wrong study design: no RCT
Bedi M, Singh R, Charlson JA, Kelly T, Johnstone C, Wooldridge A, Hackbarth DA, Moore N, Neilson JC, King DM. Is 5 the New 25? Long-Term Oncologic Outcomes From a Phase II, Prospective, 5-Fraction Preoperative Radiation Therapy Trial in Patients With Localized Soft Tissue Sarcoma. Adv Radiat Oncol. 2022 Jan 25;7(3):100850. doi: 10.1016/j.adro.2021.100850. PMID: 35647402; PMCID: PMC9133395.	no comparison between RT vs no RT (concerns the effect of RT in 5 fractions every other day)
Bonvalot S, Gronchi A, Le Péchoux C, Swallow CJ, Strauss D, Meeus P, van Coevorden F, Stoldt S, Stoeckle E, Rutkowski P, Rastrelli M, Raut CP, Hompes D, De Paoli A, Sangalli C, Honoré C, Chung P, Miah A, Blay JY, Fiore M, Stelmes JJ, Dei Tos AP, Baldini EH, Litière S, Marreaud S, Gelderblom H, Haas RL. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020 Oct;21(10):1366-1377. doi: 10.1016/S1470-2045(20)30446-0. Epub 2020 Sep 14. PMID: 32941794.	Wrong comparison (included for other RT module)
Bonvalot S, Rutkowski PL, Thariat J, Carrère S, Ducassou A, Sunyach MP, Agoston P, Hong AM, Mervoyer A, Rastrelli M, Moreno V, Li RK, Tiangco BJ, Herráez AC, Gronchi A, Sy-Ortin T, Hohenberger P, de Baère T, Cesne AL, Helfre S, Saada-Bouzid E, Anghel RM, Kantor G, Montero A, Loong HH, Vergés R, Kacso G, Austen L, Servois VF, Wardelmann E, Dimitriu M, Said P, Lazar AJ, Bovée JVMG, Péchoux CL, Pápai Z. Final Safety and Health-Related Quality of LIfe	wrong comparison (NBTXR+RT vs RT)

Results of the Phase 2/3 Act.In.Sarc Study With Preoperative NBTXR3 Plus Radiation Therapy Versus Radiation Therapy in Locally Advanced Soft-Tissue Sarcoma. Int J Radiat Oncol Biol Phys. 2022 Nov 1;114(3):422-432. doi: 10.1016/j.ijrobp.2022.07.001. Epub 2022 Jul 16. PMID: 35850363.	
Boughzala-Bennadji R, Stoeckle E, Le Péchoux C, Méeus P, Honoré C, Attal J, Duffaud F, De Pinieux G, Bompas E, Thariat J, Leroux A, Bertucci F, Isambert N, Delcambre C, Blay JY, Sunyach MP, Coindre JM, Sargos P, Penel N, Bonvalot S. Localized Myxofibrosarcomas: Roles of Surgical Margins and Adjuvant Radiation Therapy. Int J Radiat Oncol Biol Phys. 2018 Oct 1;102(2):399-406. doi: 10.1016/j.ijrobp.2018.05.055. Epub 2018 Jun 2. PMID: 30191871.	wrong study design: no RCT
Chang X, Li Y, Xue X, Zhou H, Hou L. The current management of alveolar soft part sarcomas. Medicine (Baltimore). 2021 Aug 6;100(31):e26805. doi: 10.1097/MD.0000000000026805. PMID: 34397835; PMCID: PMC8341245.	wrong study design: no systematic review
Chen YT, Tu WT, Lee WR, Huang YC. The efficacy of adjuvant radiotherapy in dermatofibrosarcoma protuberans: a systemic review and meta-analysis. J Eur Acad Dermatol Venereol. 2016 Jul;30(7):1107-14. doi: 10.1111/jdv.13601. Epub 2016 Feb 16. PMID: 26879523.	wrong study design: no RCT
Cheng H, Miura JT, Lalehzari M, Rajeev R, Donahue AE, Bedi M, Gamblin TC, Turaga KK, Johnston FM. Neoadjuvant radiotherapy for retroperitoneal sarcoma: A systematic review. J Surg Oncol. 2016 May;113(6):628-34. doi: 10.1002/jso.24221. Epub 2016 Mar 16. PMID: 26990903.	wrong comparison
Correa R, Gómez-Millán J, Lobato M, Fernández A, Ordoñez R, Castro C, Lupiañez Y, Medina JA. Radiotherapy in soft-tissue sarcoma of the extremities. Clin Transl Oncol. 2018 Sep;20(9):1127-1135. doi: 10.1007/s12094-018-1848-x. Epub 2018 Feb 23. PMID: 29476322.	wrong study aim: describe current standard of treatment
De Amorim Bernstein K, Delaney TF. Role of radiation therapy for non-extremity soft tissue sarcomas. J Surg Oncol. 2015 Apr;111(5):604-14. doi: 10.1002/jso.23863. Epub 2014 Dec 29. PMID: 25556548.	no systematic search
Diamantis A, Baloyiannis I, Magouliotis DE, Tolia M, Symeonidis D, Bompou E, Polymeneas G, Tepetes K. Perioperative radiotherapy versus surgery alone for retroperitoneal sarcomas: a systematic review and meta-analysis. Radiol Oncol. 2020 Feb 29;54(1):14-21. doi: 10.2478/raon-2020-0012. PMID: 32114526; PMCID: PMC7087419.	SR does not include RCTs
Dunst J. Prä- oder postoperative Strahlentherapie bei retroperitonealen Sarkomen unverzichtbar [Pre- or postoperative radiotherapy essential for the treatment of retroperitoneal sarcomas]. Strahlenther Onkol. 2016 Nov;192(11):820-822. German. doi: 10.1007/s00066-016-1042-4. PMID: 27596218.	wrong language
Gervais MK, Callegaro D, Gronchi A. The evolution of adjuvant/neoadjuvant trials for resectable localized sarcoma. J Surg Oncol. 2022 Jan;125(1):17-27. doi: 10.1002/jso.26745. PMID: 34897708.	not a systematic review

Guadagnolo BA, Bassett RL, Mitra D, Farooqi A, Hempel C, Dorber C, Willis T, Wang WL, Ratan R, Somaiah N, Benjamin RS, Torres KE, Hunt KK, Scally CP, Keung EZ, Satcher RL, Bird JE, Lin PP, Moon BS, Lewis VO, Roland CL, Bishop AJ. Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2022 Dec;23(12):1547-1557. doi: 10.1016/S1470-2045(22)00638-6. Epub 2022 Nov 4. PMID: 36343656; PMCID: PMC9817485.	no comparison (concerns the safety of a shorter regimen)
Haas RL, Miah AB, LePechoux C, DeLaney TF, Baldini EH, Alektiar K, O'Sullivan B. Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies. Radiother Oncol. 2016 Apr;119(1):14-21. doi: 10.1016/j.radonc.2015.12.002. Epub 2015 Dec 21. PMID: 26718153; PMCID: PMC5506844.	wrong study design: critical review
Hoefkens F, Dehandschutter C, Somville J, Meijnders P, Van Gestel D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. Radiat Oncol. 2016 Oct 12;11(1):136. doi: 10.1186/s13014-016-0668-9. PMID: 27733179; PMCID: PMC5062836.	wrong study design: no systematic review
Kannan S, Chong HH, Chew B, Ferguson JD, Galloway E, McCulloch T, Rankin KS, Ashford RU. Leiomyosarcoma in the extremities and trunk wall: systematic review and meta-analysis of the oncological outcomes. World J Surg Oncol. 2022 Apr 18;20(1):124. doi: 10.1186/s12957-022-02584-4. PMID: 35436892; PMCID: PMC9014567.	wrong research aim (prognostic impact of markers)
Kelly KJ, Yoon SS, Kuk D, Qin LX, Dukleska K, Chang KK, Chen YL, Delaney TF, Brennan MF, Singer S. Comparison of Perioperative Radiation Therapy and Surgery Versus Surgery Alone in 204 Patients With Primary Retroperitoneal Sarcoma: A Retrospective 2-Institution Study. Ann Surg. 2015 Jul;262(1):156-62. doi: 10.1097/SLA.0000000000001063. PMID: 26061213; PMCID: PMC4465112.	wrong study design: no RCT
Kungwengwe G, Clancy R, Vass J, Slade R, Sandhar S, Dobbs TD, Bragg TWH. Preoperative versus Post-operative Radiotherapy for Extremity Soft tissue Sarcoma: a Systematic Review and Meta-analysis of Long-term Survival. J Plast Reconstr Aesthet Surg. 2021 Oct;74(10):2443-2457. doi: 10.1016/j.bjps.2021.05.043. Epub 2021 Jun 9. PMID: 34266806.	SR includes only 1 RCT, included separately
Lane WO, Cramer CK, Nussbaum DP, Speicher PJ, Gulack BC, Czito BG, Kirsch DG, Tyler DS, Blazer DG 3rd. Analysis of perioperative radiation therapy in the surgical treatment of primary and recurrent retroperitoneal sarcoma. J Surg Oncol. 2015 Sep;112(4):352-8. doi: 10.1002/jso.23996. Epub 2015 Aug 4. PMID: 26238282.	wrong study design: no RCT
Lansu J, Bovée JVMG, Braam P, van Boven H, Flucke U, Bonenkamp JJ, Miah AB, Zaidi SH, Thway K, Bruland ØS, Baldini EH, Jebsen NL, Scholten AN, van den Ende PLA, Krol ADG, Ubbels JF, van der Hage JA, van Werkhoven E, Klomp HM, van der Graaf WTA, van Coevorden F, Schrage Y, van Houdt WJ, Haas RL. Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma: A Nonrandomized	wrong comparison (concerns dose reduction instead of RT vs no RT)

Controlled Trial. JAMA Oncol. 2021 Jan 1;7(1):e205865. doi: 10.1001/jamaoncol.2020.5865. Epub 2021 Jan 21. PMID: 33180100; PMCID: PMC7662477.	
Lansu J, Braam PM, van Werkhoven E, Scholten AN, Schrage Y, van Houdt WJ, van Langevelde K, Haas RL. A moderate dose of preoperative radiotherapy may improve resectability in myxoid liposarcoma. Eur J Surg Oncol. 2021 Oct;47(10):2633-2639. doi: 10.1016/j.ejso.2021.06.020. Epub 2021 Jun 23. PMID: 34233858.	no comparison between RT vs no RT (concerns the effect of a moderate radiotherapy dose on resectability)
Lazarev S, McGee H, Moshier E, Ru M, Demicco EG, Gupta V. Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: Nationwide patterns of care and trends in utilization. Pract Radiat Oncol. 2017 Nov-Dec;7(6):e507-e516. doi: 10.1016/j.prro.2017.04.010. Epub 2017 Apr 18. PMID: 28551391; PMCID: PMC6004789.	wrong study design: no RCT
Levy A, Honoré C, Dumont S, Bourdais R, Cavalcanti A, Faron M, Ngo C, Haddag-Miliani L, Le Cesne A, Mir O, Le Péchoux C. Radiothérapie préopératoire versus postopératoire dans les sarcomes des tissus mous : état des lieux et perspectives [Preoperative versus postoperative radiotherapy in soft tissue sarcomas: State of the art and perspectives]. Bull Cancer. 2021 Sep;108(9):868-876. French. doi: 10.1016/j.bulcan.2021.03.012. Epub 2021 Jul 8. PMID: 34246458.	wrong language
Li X, Dong R, Xiao M, Min L, Luo C. Neoadjuvant radiotherapy for resectable retroperitoneal sarcoma: a meta-analysis. Radiat Oncol. 2022 Dec 28;17(1):215. doi: 10.1186/s13014-022-02159-3. PMID: 36578082; PMCID: PMC9795731.	SR includes only 1 RCT, included separately
Li X, Wu T, Xiao M, Wu S, Min L, Luo C. Adjuvant therapy for retroperitoneal sarcoma: a meta-analysis. Radiat Oncol. 2021 Oct 7;16(1):196. doi: 10.1186/s13014-021-01774-w. PMID: 34620197; PMCID: PMC8496039.	SR does not include RCTs
Müller DA, Beltrami G, Scoccianti G, Frenos F, Capanna R. Combining limb-sparing surgery with radiation therapy in high-grade soft tissue sarcoma of extremities - Is it effective? Eur J Surg Oncol. 2016 Jul;42(7):1057-63. doi: 10.1016/j.ejso.2016.02.004. Epub 2016 Feb 12. PMID: 26924784.	wrong study design: no RCT
Neugebauer J, Blum P, Keiler A, Süß M, Neubauer M, Moser L, Dammerer D. Brachytherapy in the Treatment of Soft-Tissue Sarcomas of the Extremities-A Current Concept and Systematic Review of the Literature. Cancers (Basel). 2023 Feb 10;15(4):1133. doi: 10.3390/cancers15041133. PMID: 36831476; PMCID: PMC9954233.	wrong intervention, only qualitative analysis
Nussbaum DP, Rushing CN, Lane WO, Cardona DM, Kirsch DG, Peterson BL, Blazer DG 3rd. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol. 2016 Jul;17(7):966-975. doi: 10.1016/S1470-2045(16)30050-X. Epub 2016 May 17. PMID: 27210906.	wrong study design: no RCT
Qu X, Lubitz CC, Rickard J, Bergeron SG, Wasif N. A Meta-Analysis of the Association Between Radiation Therapy and Survival for Surgically Resected Soft-Tissue Sarcoma. Am J	SR only includes 1 relevant RCT, included separately

Clin Oncol. 2018 Apr;41(4):348-356. doi: 10.1097/COC.0000000000000274. PMID: 26886948.	
Ramey SJ, Yechieli R, Zhao W, Kodiyan J, Asher D, Chinea FM, Patel V, Reis IM, Wang L, Wilky BA, Subhawong T, Trent JC 2nd. Limb-sparing surgery plus radiotherapy results in superior survival: an analysis of patients with high-grade, extremity soft-tissue sarcoma from the NCDB and SEER. Cancer Med. 2018 Sep;7(9):4228-4239. doi: 10.1002/cam4.1625. Epub 2018 Jul 20. PMID: 30030882; PMCID: PMC6144142.	wrong study design: no RCT
van Praag VM, Rueten-Budde AJ, Jeys LM, Laitinen MK, Pollock R, Aston W, van der Hage JA, Dijkstra PDS, Ferguson PC, Griffin AM, Willeumier JJ, Wunder JS, van de Sande MAJ, Fiocco M. A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: Personalised sarcoma care (PERSARC). Eur J Cancer. 2017 Sep;83:313-323. doi: 10.1016/j.ejca.2017.06.032. Epub 2017 Aug 8. PMID: 28797949.	wrong study design: no RCT
Wang D, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, Petersen IA, DeLaney TF, Freeman CR, Finkelstein SE, Hitchcock YJ, Bedi M, Singh AK, Dundas G, Kirsch DG. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol. 2015 Jul 10;33(20):2231-8. doi: 10.1200/JCO.2014.58.5828. Epub 2015 Feb 9. PMID: 25667281; PMCID: PMC4486342.	wrong study design: no RCT
Willeumier JJ, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, Dijkstra PD, Ferguson PC, Griffin AM, Wunder JS, Fiocco M, van de Sande MA. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. BMJ Open. 2017 Feb 14;7(2):e012930. doi: 10.1136/bmjopen-2016-012930. PMID: 28196946; PMCID: PMC5318556.	wrong study design: no RCT
Yang X, Zhang L, Yang X, Yu W, Fu J. Oncologic outcomes of pre- versus post-operative radiation in Resectable soft tissue sarcoma: a systematic review and meta-analysis. Radiat Oncol. 2020 Jun 23;15(1):158. doi: 10.1186/s13014-020-01600-9. PMID: 32576267; PMCID: PMC7310344.	SR includes only 1 RCT, included separately

Zoekverantwoording

Voor deze vraag is gezocht met de volgende concepten: Wekedelentumoren, specifiek sarcomen EN radiotherapie EN chirurgie.

In de databases Embase en Ovid/Medline is op 15-5-2023 met relevante zoektermen gezocht vanaf 2000 naar systematische reviews en cinical trials en RCTs over radiotherapie en chirurgie bij wekedelen sarcoom. De literatuurzoekactie leverde 699 unieke treffers op.

Zoekopbrengst

Vanaf 2015 23-6-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs			211

RCTs			488
Observationele studies			
Overig			
Totaal			699
15-5-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	275	186	312
RCTs	661	627	1002
Observationele studies			
Overig			
Totaal			1314

Zoekstrategie

Embase

No.	Query	Results
#22	#5 AND #13 AND #21 artikel Gronchi niet gevonden	6
#21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 sleutelartikelen	7
#20	'late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma'	1
#19	'preoperative versus postoperative radiotherapy in soft-tissue sarcoma' AND 2011 AND sampath	1
#18	'individualizing the use/non-use of radiation therapy (rt) in soft tissue sarcoma (sts): when abstention is better than care'	1
#17	'complications of combined modality treatment of primary lower extremity soft tissue sarcomas'	1
#16	'preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs'	1
#15	'efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity'	1
#14	'adequate local control in high-risk soft tissue sarcoma of the extremity treated with surgery alone at a reference centre'	1
#13	#10 OR #11 OR #12	3003

#12	#5 AND (#8 OR #9) NOT #10 NOT #11	2067
#11	#5 AND #7 NOT #10 Clinical trials, RCTs	661
#10	#5 AND #6 SR	275
#9	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	14073538
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR	6767914

	studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3302394
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#5	#4 AND [2000-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	9564
#4	#1 AND #2 AND #3	15529
#3	'surgery'/exp/mj OR 'surgical patient'/exp/mj OR 'surgical risk'/exp OR 'perioperative period'/exp OR surgic*:ti,ab,kw OR surger*:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR presurg*:ti,ab,kw OR preoperati*:ti,ab,kw OR perisurg*:ti,ab,kw OR perioperati*:ti,ab,kw OR postsurg*:ti,ab,kw OR postoperati*:ti,ab,kw OR laparoscop*:ti,ab,kw OR intraoperati*:ti,ab,kw	5718949
#2	'radiotherapy'/exp/mj OR 'bioradiant therapy':ti,ab,kw OR 'bucky ray':ti,ab,kw OR 'bucky therapy':ti,ab,kw OR 'radio therapy':ti,ab,kw OR 'radio treatment':ti,ab,kw OR 'radiohypophysectomy':ti,ab,kw OR	1072427

	'radiotherapy':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'roentgen treatment':ti,ab,kw OR 'rontgen therapy':ti,ab,kw OR 'therapeutic radiology':ti,ab,kw OR 'x radiotherapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw OR 'x-ray therapy':ti,ab,kw OR irradiati*:ti,ab,kw OR radiati*:ti,ab,kw	
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)	106090

Ovid/Medline

#	Searches	Results
14	11 or 12 or 13	2479
13	((8 or 9) and 10) not 11 not 12	1666
12	(7 and 10) not 11 Clinical trials, RCT	627
11	6 and 10 SR	186
10	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	4696
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1	5422320

	active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4436464
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2587457
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*)	667693

	adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
5	limit 4 to yr="2000 -Current"	4853
4	1 and 2 and 3	6598
3	exp Radiotherapy/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,ab,kf.	811912
2	exp Surgical Procedures, Operative/ or exp Specialties, Surgical/ or su.fs. or exp Perioperative Period/ or surgic*.ti,ab,kf. or surger*.ti,ab,kf. or operation*.ti,ab,kf. or operative.ti,ab,kf. or presurg*.ti,ab,kf. or preoperati*.ti,ab,kf. or perisurg*.ti,ab,kf. or perioperati*.ti,ab,kf. or postsurg*.ti,ab,kf. or postoperati*.ti,ab,kf. or laparoscop*.ti,ab,kf.	5516780
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 sarcoma*).ti,ab,kf.	54351

Module 4.4 – Eerstelijns-chemotherapie

Search and select
A systematic review of the literature was performed to answer the following question: What is the effectivity and safety of first-line chemotherapy X compared to first-line chemotherapy Y in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcoma?

P	**(Patients)**	: patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas
I	**(Intervention)**	: first-line chemotherapy X
C	**(Comparison)**	: first-line chemotherapy Y (doxo/anthracyclines)
O	**(Outcomes)**	: overall survival, progression-free survival, response rate, quality of life, safety

Relevant outcome measures
The guideline development group considered overall survival as a critical outcome measure for decision making; and progression-free survival, response rate, quality of life, and safety (adverse events) as important outcome measures for decision making.

A priori, the working group did not define the outcome measures overall survival, progression-free survival, response rate and quality of life but used the definitions used in the studies. Safety was defined as adverse events such as febrile neutropenia, cardiotoxicity, stomatitis, fatigue

The working group defined the minimal clinically (patient) important differences for the outcomes overall survival based on the PASKWIL criteria (NVMO, 2023) and for the other outcomes based on relevant literature:
It should however be noted that PASKWIL criteria apply to new drugs and none of the drugs below are considered as new drugs anymore.

- Overall survival:
  - Median OS control group ≤12 months: >12 weeks benefit and Hazard Ratio (HR) <0.7
  - Median OS control group >12 months: >16 weeks benefit and Hazard Ratio (HR) <0.7
- Progression free survival: HR < 0.60.
- Response rate: 25% difference, Risk ratio (RR) <0.8 or >1.25
- Quality of life: The minimum important difference (MID) has been estimated to be a difference of 0.08 or more points for the EQ-5D utility index and seven or more points for the EQ-5D VAS (Pickard, 2007). For quality of life measured with the EORTC QLQ-C30, a difference of 10 points was considered as a clinical important difference (Fiteni, 2016)
- Safety: adverse events including wound complications, lethal >5%, acute or severe >25%.

Search and select (Methods)
The databases Ovid/Medline, Embase were searched with relevant search terms from 2015 until 6 June 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 495 hits. Subsequently, the references of the ESMO EURACAN GENTURIS Clinical Practice Guidelines (2021) were searched for additional relevant studies published before 2015. Studies were selected based on the following criteria:

- Study design: randomized controlled trial or systematic review.
- Patients with locally advanced or metastatic soft tissue sarcoma who received first line chemotherapy.

- Comparing doxorubicin with a different type of chemotherapy (available in the Netherlands).
- Describing at least one of the relevant outcomes specified in the PICO.
- Published from 2015.

A total of 34 studies were initially selected based on title and abstract screening. After reading the full text, 24 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 5 studies were included. Subsequently, the references of the ESMO guidelines for soft tissue and visceral sarcomas (Gronchi, 2021) were searched for additional relevant studies published before 2015. As a result, one additional study was included (Judson, 2014).

Results

Six studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Six studies were included in the analysis of the literature. All studies are randomized controlled trials comparing first-line treatment with doxorubicin alone with either a combination of doxorubicin and a different type of chemotherapy or a different type of chemotherapy as a substitution of doxorubicin. Not all studies were phase 3 studies. Relevant study characteristics are presented in Table 1.

Table 1 – Study characteristics

Study	Patients (C; I): n, age, sex	Type of study	Type of sarcoma	Intervention	Comparison
Doxorubicin add-on					
Pautier, 2022	76; 74, median age 64; 59 years, F/M 59/17; 53/21	Phase 3 trial	metastatic or unresectable **leiomyosarcoma**	**doxorubicin** (60 mg/m²) and 1·1 mg/m² **trabectedin** every 3 weeks for a maximum of six cycles, followed by trabectedin maintenance treatment	doxorubicin (75mg/m²) alone once every 3 weeks for up to six cycles
Martin-Broto, 2015	59; 54, median age 52; 53 years, F/M 29/30; 22/32	Phase 2 study	locally advanced non-resectable or metastatic STS	**trabectedin** as a 3-hour infusion at 1.1 mg/m^2, combined with **doxorubicin** 60 mg/m^2 for six cycles	doxorubicin at 75mg/m^2 for six cycles
Judson, 2014	228; 227, median age 48, 47 years, F/M 125/103; 113/114	Phase 3 trial	locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma	**doxorubicin** 25 mg/m² per day on days 1–3 and **ifosfamide** (2·5 g/m² per day, days 1–4) plus mesna (0·5 g/m² followed by pegfilgrastim (6 mg, day 5) every 3 weeks for a maximum of six cycles	doxorubicin 75 mg/m² on day 1 every 3 weeks for a maximum of six cycles
Doxorubicin substitution					
Bui-Nguyen, 2015	3 groups: 43; 47; 43, median age 60; 60; 60	Phase IIb study	advanced/ metastatic soft-tissue sarcoma	T3h group: **trabectedin** 1.3 mg/m^2/3-hour intravenous infusion on day 1 every 3 weeks	doxorubicin 75 mg/m^2 on day 1 every 3 weeks

	years, male: 18; 18; 20			T24h group: **trabectedin** 1.5 mg/m^2/24 hour intravenous infusion on day 1 every 3 weeks	
Grunwald, 2020	39/81, median age 70; 72 years, F/M 22/17; 37/44	Phase II study	progressive advanced or metastatic STS (in elderly patients > 60 years)	**pazopanib** 800 mg once per day until progression or intolerance	doxorubicin 75 mg/m^2 once every 3 weeks intravenously for up to 6 cycles
Seddon, 2017	129;128; median age 56; 55 years, F/M 79/50; 77/51	Phase 3 trial	advanced unresectable or metastatic soft-tissue sarcomas	**gemcitabine** 675 mg/m² on day 1 and gemcitabine 675 mg/m² followed by **docetaxel** 75 mg/m² on day 8 every 3 weeks	doxorubicin 75 mg/m² on day 1 every 3 weeks

Results

Overall survival

Doxorubicin add-on

Doxorubicin and trabectedin in leiomyosarcoma

Pautier (2022) reported an overall survival of 26 (34.2%) patients in the doxorubicin alone group and 32 (43.2%) patients in the doxorubicin plus trabectedin group, over the length of 48 months follow-up. The RR of 0.79 (95% CI 0.53 to 1.19) is not considered clinically relevant.

Doxorubicin and trabectedin in soft tissue sarcomas

Martin-Broto (2016) reported a median overall survival of 13.7 months in the doxorubicin group and 13.3 months in the doxorubicin plus trabectedin group. The HR of 1.21 (95% CI 0.77 to 1.92) is not considered clinically relevant.

Doxorubicin and ifosfamide

Judson (2014) reported a median overall survival of 12.8 months (95% CI 10.5 to 14.3) in the doxorubicin group and 14.3 months (95% CI 12.5 to 16.5 months) in the doxorubicin and ifosfamide group. The HR of 0.83 (95% CI 0.67 to 1.03) is not considered clinically relevant.

Doxorubicin substitution

Trabectedin

Bui-Nguyen (2015) reported that at the time of analysis, 36 patients had died (16 in the T3h group (34%); 10 in the T24h group (23.3%); and 10 in the doxorubicin group (23.3%)). For T24h versus doxorubicin the HR of 0.94 (95% CI 0.39 to 2.25) is not considered clinically relevant while for T3h versus doxorubicin the HR of 1.30 (95% CI 0.58 to 2.90) is clinically relevant in favor of the doxorubicin group.

Pazopanib

Grunwald (2020) studied patients aged 60 years or older and reported an overall survival at 12 weeks of 14.3 months (95% CI 8.3 to 25.9) in the doxorubicin group and 12.3 (95% CI 8.7 to 19.8) in the pazopanib group. This difference was not considered clinically relevant. Median overall survival was 12.3 months (IQR 6.0 to 25.8 months) in the pazopanib group and 14.3 months (IQR 7.1 to 27.0 months) in the doxorubicin group. The HR of 1.08 (95% CI 0.68 to 1.72) is not clinically relevant.

Gemcitabine and docetaxel

Seddon (2017) reported an overall survival of 86.8% (95% CI 79.6 to 91.6) in the doxorubicin group, and 82.6% (95% CI 74.8 to 88.2) in the gemcitabine and docetaxel group at 24 weeks after randomization. Median overall survival was 76.3 weeks (95% CI 60.0 to 91.3) in the doxorubicin group and 67.3 weeks (95% CI 53.1 to 83.1) in the gemcitabine and docetaxel Group. The HR of 1.14 (95% CI 0.83 to 1.57) is not clinically relevant.

Progression-free survival

Doxorubicin add-on

Doxorubicin and trabectedin in leiomyosarcoma

Pautier (2022) reported a progression free survival rate at 12 months of 16.0% (95% CI 9.4 to 25.9) in the doxorubicin group and 50.7% (95% CI 39.5 to 61.9) in the doxorubicin plus trabectedin group. Additionally, at 24 months of follow-up, progression-free survival rates of 5.3% (95% CI 2.1 to 12.9) and 30.2% (95% CI 20.9 to 41.5) were reported for respectively the doxorubicin and doxorubicin plus trabectedin group. Median progression-free survival was 6.2 months (95 % CI, 4.1 to 7.1) in the doxorubicin group, and 12.2 months (95% CI, 10.1 to 15.6) in the doxorubicin plus trabectedin group. The adjusted HR of 0.41 (95% CI 0.29 to 0.58) is considered clinically relevant in favor of the doxorubicin plus trabectedin group.

Doxorubicin and trabectedin soft tissue sarcomas

Martin-Broto (2016) reported progression-free survival for both groups. Median progression-free survival was 5.5 months in the doxorubicin group, and 5.7 months in the doxorubicin plus trabectedin group. The HR of 1.16 (95% CI 0.79 to 1.71) is not considered clinically relevant.

Doxorubicin and ifosfamide

Judson (2014) reported a median progression free survival of 4.6 months (95% CI 2.9 to 5.6) in the doxorubicin group and 7.4 months (95% CI 6.6 to 8.3) in the doxorubicin and ifosfamide group. The HR of 0.74 (95% CI 0.60–0.90) is not considered clinically relevant.

Doxorubicin substitution

Trabectedin

Bui-Nguyen (2015) presented Kaplan-Meier curves for progression-free survival. Median progression-free survival was 5.5 months in the doxorubicin group, 2.8 months in the trabectedin 3h group, and 3.1 months in the trabectedin 24h group. The HR of 1.50 (95% CI 0.91 to 2.48) for doxorubicin vs trabectedin 3h is clinically relevant in favor of the doxorubicin group. The HR of 1.13 (95% CI 0.67 to 1.90) for doxorubicin vs trabectedin 24h is not clinically relevant.

Pazopanib

Grunwald (2020) reported that patients in the doxorubicin group achieved a progression free survival rate of 44% (95% CI 28 to 59) at 12 weeks, and patients in the pazopanib group achieved a progression-free survival rate of 53% (95% CI 42 to 64). At 26 weeks, patients in the doxorubicin group achieved a progression free survival rate of 23% (95% CI 10 to 36) and in the pazopanib group patients achieve a progression free survival rate of 26% (95% CI 16 to 35). Median progression-free survival was 4.4 months (95% CI, 2.7 to 6.0 months) in the pazopanib group and 5.3 months (95% CI, 1.7 to 8.2 months) in the doxorubicin group. The HR of 1.00 (95% CI 0.65 to 1.53) is not clinically relevant.

Gemcitabine and docetaxel

Seddon (2017) reported progression-free survival at 12 weeks of 72.1% (95% CI 63.5 to 79.0) in the doxorubicin group and 63.8% (95% CI 54.8 to 71.5) in the gemcitabine and docetaxel group. At 24 weeks, the progression-free survival was respectively 46.3% (95% CI 37.5 to 54.6)

and 46.4% (95% CI 37.5 to 54.8) in the doxorubicin and gemcitabine and docetaxel group. Median progression-free survival was 23.3 weeks (95% CI 19.6 to 30.4) in the doxorubicin group and 23.7 weeks (95% CI 18.1 to 20.0) in the gemcitabine and docetaxel group. The HR of 1.28 (95% CI 0.99 to 1.65) is not clinically relevant.

Response rate

Doxorubicin add-on

Doxorubicin and trabectedin in leiomyosarcoma

Pautier (2022) reported ten (13%) partial and complete responses in the doxorubicin group compared to twenty-seven (36%) partial and complete responses in the doxorubicin plus trabectedin group, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The RR of 0.36 (95% CI 0.19 to 0.69) is considered clinically relevant in favor of the doxorubicin plus trabectedin group.

Doxorubicin and trabectedin in soft tissue sarcomas

Martin-Broto (2016) observed solely partial responses, and observed a partial response in 10 (17%) patients in the doxorubicin group and 9 (17%) patients in the doxorubicin plus trabectedin group. The RR of 1.02 (95% CI 0.45 to 2.31) is not considered clinically relevant.

Doxorubicin and ifosfamide

Judson (2014) observed objective response rates in 31 (14%) patients in the doxorubicin group and 60 (26%) patients in the doxorubicin and ifosfamide group. The RR of 0.51 (95% CI 0.35 to 0.76) is considered clinically relevant in favor of the doxorubicin and ifosfamide group.

Doxorubicin substitution

Trabectedin

Bui-Nguyen (2015) reported respectively among 27 (62.8%) and 52 (57.8%) patients in the doxorubicin and trabectedin (stabilization or partial/complete) responses. The RR of 1.09 (95% CI 0.81 to 1.45) is not considered clinically relevant.

Pazopanib

Grunwald (2020) observed objective response rates (partial plus complete) of 6 (15.4%) patients in the doxorubicin group, and 10 (12.3%) in the pazopanib group. The RR of 1.25 (95% CI 0.49 to 3.18) is considered clinically relevant in favor of the pazopanib group.

Gemcitabine and docetaxel

Seddon (2017) observed response rates in 25 (19%) patients in the doxorubicin group, and 25 (20%) patients in the gemcitabine and docetaxel group, by local investigators according to RECIST (complete or partial response). The RR of 0.99 (95% CI 0.60 to 1.63) is not considered clinically relevant.

Quality of life

Doxorubicin add-on

Doxorubicin and trabectedin in leiomyosarcoma

Pautier (2022) did not report the outcome quality of life.

Doxorubicin and trabectedin in soft tissue sarcomas

Martin-Broto (2016) did not report the outcome quality of life.

Doxorubicin and ifosfamide

Judson (2014) did not report the outcome quality of life.

Doxorubicin substitution
Trabectedin
Bui-Nguyen (2015) did not report the outcome quality of life.

Pazopanib
Grunwald (2020) reported on global health status using the EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (30-item) Quality of Life Questionnaire; the (EORTC QLQ-C30) to assess global HR-QoL in patients with cancer (not specified scale scoring). However, only baseline QoL scores were reported.

Gemcitabine and docetaxel
Seddon (2017) had insufficient questionnaires returned in order to assess quality of life at 18 weeks. Quality-of-life measures did not differ between the treatment groups at 12 weeks post-randomization.

Safety (adverse events and toxicity)
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
Pautier (2022) reported adverse events (grade 3-4) using the National Cancer Institute Common Terminology Criteria for Adverse Events among 39 (52%) and 71 (96%) of the patients in respectively the doxorubicin and doxorubicin plus trabectedin group, with most of these being hematological events (neutropenia, anemia, thrombocytopenia, and febrile neutropenia). The RD of -0.45 (95% CI -0.57 to -0.33) is considered clinically relevant in favor of the doxorubicin group. Additionally, in the doxorubicin and doxorubicin plus trabectedin group, 3 (4%) and 17 (23%) of the patients stopped treatment because of toxicity. The RD of -0.19 (95% CI -0.30 to -0.08) is not considered clinically relevant.

Doxorubicin and trabectedin in soft tissue sarcomas
Martin-Broto (2016) reported adverse events in accordance with the National Cancer Institute's common Terminology Criteria for Adverse Events version 3.0, see Table 2. The differences between the groups with regard to these adverse events are not clinically relevant.

Table 2 – Adverse events: worst toxicity by patient, grade 3 or 4

Type of adverse event	Doxorubicin group (n=59)	Doxorubicin + trabectedin group (n=54)
Thrombopenia	2%	18%
Neutropenia	36%	55%
Nausea	2%	8%
Stomatitis	0%	8%
Febrile neutropenia	24%	32%

Doxorubicin and ifosfamide
Judson (2014) reported Grade 3 and 4 toxic effects graded according to International Common Toxicity Criteria. Some adverse events (Grade 3-4) listed and reported were: leucopenia, neutropenia, febrile neutropenia, anemia, and thrombocytopenia, see Table 5. The differences between the groups with regard to leucopenia, febrile neutropenia, anemia and thrombocytopenia are clinically relevant in favor of the doxorubicin group. For neutropenia the difference is not considered clinically relevant.

Table 5 – Adverse events, grade 3-4

Type of adverse event	Doxorubicin group (n=228)	Doxorubicin + ifosfamide group (n=227)
Leucopenia	40 (18%)	97 (43%)

Neutropenia	83 (37%)	93 (42%)
Febrile neutropenia	30 (13%)	103 (46%)
Anemia	10 (5%)	78 (35%)
Thrombocytopenia	1 (<1%)	75 (33%)

Doxorubicin substitution
Trabectedin
Bui-Nguyen (2015) reported various adverse events (grade 3-4), see Table 5. The differences between the groups with regard to these adverse events are not clinically relevant.

Table 6 – Adverse events, grade 3-4

Type of adverse event	Doxorubicin group (n=40)	Trabectedin groups (n=87)
Nausea	2 (5.0%)	8 (8.9%)
Febrile neutropenia	3 (7.5%)	11 (12.2%)
Thrombocytopenia	1 (2.5%)	14 (15.6%)
Neutropenia	23 (57.5%)	41 (45.6%)
Fatigue	2 (5.0%)	6 (6.7%)

Toxicity was reported in 1 (2.5%) and 15 (16.7%) patients in the doxorubicin and trabectedin groups. The RD of -0.10 (95% CI -0.25 to 0.05) is not considered clinically relevant.

Pazopanib
Grunwald (2020) reported any event (Grade 3-4) according to the classification of the Common Terminology Criteria for Adverse Events (CTCAE 4.0) in 35 (94.6%) of the patients in the doxorubicin group, and 66 (81.5%) of the patients in the pazopanib group. The RD of 0.08 (95% CI -0.04 to 0.21) is not considered clinically relevant.
Treatment-related severe adverse events were respectively reported among 10 (27%) of the patients in the doxorubicin group, and 27 (33.3%) of the patients in the pazopanib group. The difference of -6.3% is not clinically relevant.

Gemcitabine and docetaxel
Seddon (2017) reported adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The three most common Grade 3-4 serious adverse events were febrile neutropenia, fever, and neutropenia, see Table 7. The differences between the groups with regard to these adverse events are not clinically relevant.

Table 7 – Adverse events, grade 3-4

Type of adverse event	Doxorubicin group (n=40)	Trabectedin groups (n=87)
Febrile neutropenia	27 (17%)	15 (12%)
Fever	18 (12%)	19 (15%)
Neutropenia	22 (14%)	10 (8%)

Level of evidence of the literature
The level of evidence for all outcomes was based on randomized controlled trials and therefore started at high.

Overall survival
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of study design (open-label study) (risk of bias, -1), and OIS not met (imprecision, -1).

Doxorubicin and trabectedin in soft tissue sarcomas
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of study design (open-label study) (risk of bias, -1), and OIS not met (imprecision, -1).

Doxorubicin and ifosfamide
For the outcome measure **overall survival**, the level of evidence was downgraded by two levels to **low** due to study limitations (blinding not reported, risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin substitution
Trabectedin
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** because of study design (open-label study) (risk of bias, -1), and OIS not met (imprecision, -1).

Pazopanib
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels to **low** due to study limitations (no reporting of concealment of allocation and loss to follow-up) (risk of bias, -1) and OIS not met (imprecision, -1).

Gemcitabine and docetaxel
For the outcome **overall survival**, the level of evidence was downgraded by two levels to **low** due to study limitations (no blinding, risk of bias, -1) and OIS not met (imprecision, -1).

Progression-free survival
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** because of study design (open-label study) and unreported concealment of allocation (risk of bias, -1), and due to the confidence interval crossing the border of clinical relevance (imprecision, -1).

Doxorubicin and trabectedin in soft tissue sarcomas
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** because of study design (open-label study) and unreported concealment of allocation (risk of bias, -1), and due to the confidence interval crossing the border of clinical relevance (imprecision, -1).

Doxorubicin and ifosfamide
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** due to study limitations (blinding not reported, risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin substitution
Trabectedin
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** because of study design (open-label study) and unreported concealment of allocation (risk of bias, -1), and due to the confidence interval crossing the border of clinical relevance (imprecision, -1).

Pazopanib
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** due to study limitations (no reporting of concealment of allocation and loss to follow-up) (risk of bias, -1) and OIS not met (imprecision, -1).

Gemcitabine and docetaxel
The level of evidence regarding the outcome measure **progression-free survival** was downgraded by two levels to **low** due to study limitations (no blinding, risk of bias, -1) and OIS not met (imprecision, -1).

Response rate
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
The level of evidence regarding the outcome measure **response rate** was downgraded by two levels **low** because of study design (open-label study), concealment of allocation not reported (risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin and trabectedin in soft tissue sarcomas
The level of evidence regarding the outcome measure **response rate** was downgraded by two levels **low** because of study design (open-label study), concealment of allocation not reported (risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin and ifosfamide
The level of evidence regarding the outcome measure r**esponse rate** was downgraded by by two levels to **low** due to study limitations (blinding not reported, risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin substitution
Trabectedin
The level of evidence regarding the outcome measure **response rate** was downgraded by two levels **low** because of study design (open-label study), concealment of allocation not reported (risk of bias, -1) and OIS not met (imprecision, -1).

Pazopanib
The level of evidence regarding the outcome measure **response rate** was downgraded by three levels to **very low** due to study limitations (no reporting of concealment of allocation and loss to follow-up) (risk of bias, -1) and the confidence interval crossing the border of clinical relevance on both sides (imprecision, -2).

Gemcitabine and docetaxel
The level of evidence regarding the outcome measure **response rate** was downgraded by two levels to **low** due to study limitations (no blinding, risk of bias, -1) and OIS not met (imprecision, -1).

Quality of life
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
As none of the included studies reported data on **quality of life,** it was not possible to determine the level of evidence.

Doxorubicin and trabectedin in soft tissue sarcomas
As none of the included studies reported data on **quality of life,** it was not possible to determine the level of evidence.

Doxorubicin and ifosfamide
As none of the included studies reported data on **quality of life,** it was not possible to determine the level of evidence.

Doxorubicin substitution
Trabectedin
As none of the included studies reported data on **quality of life,** it was not possible to determine the level of evidence.

Pazopanib
As none of the included studies reported data on **quality of life**, it was not possible to determine the level of evidence.

Gemcitabine and docetaxel
As none of the included studies reported data on **quality of life**, it was not possible to determine the level of evidence.

Safety
Doxorubicin add-on
Doxorubicin and trabectedin in leiomyosarcoma
The level of evidence regarding the outcome measure **safety** was downgraded by two levels to **low** because of study design (open-label study, not reporting concealment of allocation) and OIS not met (imprecision, -1).

Doxorubicin and trabectedin in soft tissue sarcomas
The level of evidence regarding the outcome measure **safety** was downgraded by two levels to **low** because of study design (open-label study, not reporting concealment of allocation) and OIS not met (imprecision, -1).

Doxorubicin and ifosfamide
The level of evidence regarding the outcome measure **safety** was downgraded by
by two levels to **low** due to study limitations (blinding not reported, risk of bias, -1) and OIS not met (imprecision, -1).

Doxorubicin substitution
Trabectedin
The level of evidence regarding the outcome measure **safety** was downgraded by two levels to **low** because of study design (open-label study, not reporting concealment of allocation) and OIS not met (imprecision, -1).

Pazopanib
The level of evidence regarding the outcome measure **safety** was downgraded by
by two levels to **low** due to study limitations (no reporting of concealment of allocation and loss to follow-up) (risk of bias, -1) and OIS not met (imprecision, -1).

Gemcitabine and docetaxel

The level of evidence regarding the outcome measure **safety** was downgraded by two levels to **low** due to study limitations (no blinding, risk of bias, -1) and OIS not met (imprecision, -1).

Conclusions

Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **doxorubicin + trabectedin** in patients with leiomyosarcoma. *Source: Pautier, 2022*
Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **doxorubicin + trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Martin-Broto, 2016*
Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **doxorubicin + ifosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Judson, 2014*
Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Bui-Nguyen, 2015*
Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **pazopanib** in elderly patients (>60 years) with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Grunwald, 2020*
Low GRADE	Doxorubicin may result in little to no difference in **overall survival** when compared with **gemcitabine and docetaxel** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Seddon, 2017*

Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **doxorubicin + trabectedin** in patients with leiomyosarcoma. *Source: Pautier, 2022; Martin-Broto, 2016*
Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **doxorubicin + trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Martin-Broto, 2016*
Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **doxorubicin + ifosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Judson, 2014*

Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Bui-Nguyen, 2015*
Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **pazopanib** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Grunwald, 2020*
Low GRADE	Doxorubicin may result in little to no difference in **progression-free survival** when compared with **gemcitabine and docetaxel** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Seddon, 2017*

Low GRADE	Doxorubicin may result in little to no difference in **response rate** when compared with **doxorubicin + trabectedin** in patients with leiomyosarcoma. *Source: Pautier, 2022*
Low GRADE	Doxorubicin may result in little to no difference in **response rate** when compared with **doxorubicin + trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Martin-Broto, 2016*
Low GRADE	Doxorubicin may result in a reduced **response rate** when compared with **doxorubicin + evofosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Tap, 2017*
Low GRADE	Doxorubicin may result in a reduced **response rate** when compared with **doxorubicin + ifosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Judson, 2014*
Low GRADE	Doxorubicin may result in little to no difference in **response rate** when compared with **trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Bui-Nguyen, 2015*
Very low GRADE	The evidence is very uncertain about the effect of doxorubicin on **response rate** when compared with **pazopanib** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Grunwald, 2020*
Low GRADE	Doxorubicin may result in little to no difference in **response rate** when compared with **gemcitabine and docetaxel** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Seddon, 2017*

NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **doxorubicin + trabectedin** in patients with leiomyosarcoma. *Source: -*
NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **doxorubicin + trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: -*
NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **doxorubicin + ifosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: -*
NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: -*
NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **pazopanib** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: -*
NO GRADE	No evidence was found regarding the effect of doxorubicin on **quality of life** when compared with **gemcitabine and docetaxel** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: -*

Low GRADE	Doxorubicin may increase **safety** when compared with **doxorubicin + trabectedin** in patients with leiomyosarcoma. *Source: Pautier, 2022*
Low GRADE	Doxorubicin may increase **safety** when compared with **doxorubicin + trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Martin-Broto, 2016*
Low GRADE	Doxorubicin may increase **safety** when compared with **doxorubicin + ifosfamide** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Judson, 2014*
Low GRADE	Doxorubicin may result in little to no difference in **safety** when compared with **trabectedin** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Bui-Nguyen, 2015*

Low GRADE	Doxorubicin may result in little to no difference in **safety** when compared with **pazopanib** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Grunwald, 2020*
Low GRADE	Doxorubicin may result in little to no difference in **safety** when compared with **gemcitabine and docetaxel** in patients with locally advanced (primary irresectable) and/or metastatic soft tissue sarcomas. *Source: Seddon, 2017*

Kennislacunes

Vanwege de vele (zeldzame) subtypes weten we niet voor elk subtype wat de beste systemische behandeling in de eerste lijn is en wat de optimale volgorde van systemische therapie is.

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	Geen nieuwe behandelvormen voorgesteld	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Pautier (2022)	Type of study: RCT (LMS-04 was a multicenter, open-label, randomized, phase 3 superiority study) Setting and country: Patients included from 20 centers of the French Sarcoma Group (anticancer centers or hospitals with an oncological unit) in France. Funding and conflicts of interest: Funding: PharmaMar. All authors declare no competing interests.	Inclusion criteria: - Patients included had histologically confirmed diagnosis by experts, -18 years or older, -eastern cooperative oncology group performance status of less than 2, -adequate haematological, liver, and cardiac functions. Exclusion criteria: -patients history of malignancy, -who were in complete remission for less than 3 years, -who had CNS metastases N total at baseline: 150 Intervention: 76 Control: 74 Important prognostic factors[2]: *For example* *Median age:* *I: 64 (53-69)* *C: 59 (52-68)* *Sex:* *I: 17/76 (22%) M* *C: 21/74 (28%) M*	Describe intervention (treatment/procedure/test): Doxorubicin alone as firstline therapy for metastatic or unresectable leiomyosarcoma (uterine or soft tissue). Patients received doxorubicin (75 mg/m²) alone once every 3 weeks for up to six cycles via the central venous route per slow perfusion for 10–15 min. An injection of subcutaneous lenograstim (granulocyte-colony stimulation factor) was given every day from day 3 to day 9. No maintenance treatment was allowed in the doxorubicin alone group. Surgery for residual disease (primary tumor or metastasis, or both) was allowed in both groups (except for progressive disease) after six cycles according to investigator decisions;	Describe control (treatment/procedure/test): doxorubicin plus trabectedin followed by trabectedin alone in patients without progression (doxorubicin plus trabectedin group) as firstline therapy for metastatic or unresectable leiomyosarcoma (uterine or soft tissue). In the doxorubicin plus trabectedin group, patients received doxorubicin (60 mg/m²) for 10–15 min via central venous perfusion followed by a 3-h central venous perfusion of 1·1 mg/m² trabectedin on day 1. Pretreatment with 20 mg dexamethasone was administered 30 min before trabectedin. An injection of pegfilgrastim (6 mg; pegylated granulocyte-colony stimulation factor) was	Length of follow-up: 48 months Loss-to-follow-up: not reported Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival[d] I: 26 (34.2%) C: 32 (43.2%) progression free survival[b] 12 months: I: 16.0% (95% CI 9.4-25.9] C: 50.7% [95% CI 39.5-61.9] 24 months: I: 5.3% [95% CI 2.1-12.9] C: 30.2% [95% CI 20.9-41.5] Median PFS: I: 6.2 months (95 % CI, 4.1 to 7.1) C: 12.2 months (95% CI, 10.1 to 15.6) Response rate, N (%)[c] *Complete and partial* I: 10 (13%) C: 27 (36%) (difference 23% [95% CI 10–37]; p=0·0009)	-Conclusion: LMS-04 met its primary endpoint, identifying a statistically significant improvement in progression-free-survival with the doxorubicin plus trabectedin combination compared with standard-of-care doxorubicin alone as a first-line treatment for metastatic leiomyosarcomas. This improvement was observed both in the uterine and the soft tissue populations. **Comments** -Clinical trial number registered. -Funding: PharmaMar. [a]= adverse events assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events.

		Groups comparable at baseline? yes	A maximum of two dose reductions for each drug were permitted.	administered on day 2 subcutaneously. Treatment was administered every 3 weeks for a maximum of six cycles. Patients in the doxorubicin plus trabectedin group without progression after six cycles of doxorubicin and trabectedin (with or without surgery) received maintenance trabectedin (1·1 mg/m²) via central venous perfusion for 3 h (even in the case of previous dose reductions of trabectedin in the combined phase with doxorubicin) after premedication with intravenous dexamethasone (20 mg). Maintenance trabectedin was administered every 3 weeks until disease progression or for a maximum period of 12 months of treatment (maximum 17 cycles in maintenance therapy), whichever occurred first. Surgery for residual disease (primary tumor or metastasis, or both) was allowed in both groups (except for progressive disease) after six cycles according to investigator decisions; A maximum of two dose reductions for each drug were permitted.		quality of life not reported safety (adverse events[a] and toxicity[e]) *Stopped treatment because of toxicity* I: 3 (4%) C: 17 (23%) *Adverse events (grade 3-4) reported* I: 39 (52%) C: 71 (96%)	[b]= progression free survival was defined as the time from random assignment until date of progression, established on the basis of RECIST criteria, or the date of death from any cause,whichever occurred first. [c]= The response rate was defined as the proportion of patients with all complete or partial responses according to RECIST criteria. The response taken into consideration was the best response during the six induction cycles. [d]= Overall survival was defined as the time from the date of random assignment to the date of death from any cause. [e]= Because maintenance with trabectedin after six cycles of the combined therapy was a new method, the toxicity was monitored in the first ten patients on maintenance in group B and was discussed with the internal data safety monitoring board.

Bui-Nguyen (2015)	Type of study: randomized multicenter prospective dose-selection (a multicenter, phase IIB study followed by a phase III study). Setting and country: Multiple centers in different countries such as United States, Austria, Belgium, Denmark, France, Germany, Hungary, the Netherlands, Poland, Slovakia, Spain, Switzerland, United Kingdom Funding and conflicts of interests: Nicolas Penel declares receiving funding from Pharmamar, Novartis, Bayer Healthcare, Roche, and Janssen Cilag and discloses a consultant or advisory role for Pharmamar and Bayer Healthcare. Jean Yves Blay	Inclusion criteria: - Eligible patients were >=18 years old, - Had one of the following histologically-confirmed advanced and/or metastatic STS of grades II/III and with progressive disease as assessed by the local investigator, - Patients had the presence of measurable disease according to response evaluation criteria in solid tumors (RECIST 1.1), - World Health Organisation (WHO) performance status (PS) 0 or 1, - Having adequate bone marrow (absolute neutrophils count (ANC) >= 1.5 X 10^9 /L, - Hemoglobin (HB) >= 9 g/dL or HB >= 5.6 mmol/L, - Platelets (PLT) P 100 >= 10^9/L), - Hepatic (bilirubin 6 ULN, alanine aminotransferase (SGPT/ALT) and aspartate aminotransferase (SGOT/AST) =< 2.5 X ULN) and renal (serum creatinine =< 1.5 X ULN) functions, - Normal left ventricular ejection fraction (LVEF) assessed by echocardiography or	Describe intervention (treatment/procedure/test): Patients with advanced/metastatic soft tissue sarcoma receiving doxorubicin hydrochloride 75 mg/m2 infusion on day 1 every 3 weeks. Treatment repeats every 3 weeks for 6 courses in the absence of disease progression or unacceptable toxicity.	Describe control (treatment/procedure/test): Patients with advanced/metastatic soft tissue sarcoma T3h investigational arm consisting of trabectedin 1.3 mg/m2 /3-hour intravenous infusion on day 1 every 3 weeks. Courses repeat every 3 weeks in the absence of disease progression or unacceptable toxicity; (ii) T24h investigational arm consisting of trabectedin 1.5 mg/m2/24 hour intravenous infusion on day 1 every 3 weeks. Courses repeat every 3 weeks in the absence of disease progression or unacceptable toxicity.	Length of follow-up: Not specified. In article stated that; ''*AEs were assessed every 6 weeks during the first 3 months and every 12 weeks thereafter. After progression, patients were followed-up every 12 weeks for survival*.'' And, ''*Median follow-up per arm was: 7.8 months (interquartile range (IQR) 5.4–10.3) doxorubicin, 8.0 months (IQR 6.4–11.3) T3h, and 7.9 months (IQR 5.7–11.3) T24h. E.g. Overall survival (start date 'June 2011 and August 2012'-the clinical cut-off date for analysis was 15th March 2013)*.'' In the phase III trial – not this study, patients complete quality of life questionnaire (EORTC QLQ-C30 version 3) at baseline, at 6, 12, 24, and 36 weeks during study, and at the end of study. After completion of study therapy, patients are followed	Outcome measures and effect size (include 95%CI and p-value if available): *For the outcome measures: T3h and T24 h were added up.* Overall survival[c] (N, %) I: 33 (76.7%). C: 64 (71.1%) Progression-free survival[b]: (N, %) *6 months:* I: 16 (38%) C: 32 (37%) *12 months* I: 8 (18%) C: 15 (17%) *Median PFS[b]* I: 5.5 months C T3H: 2.8 months C T24H: 3.1 months (objective) response rate[a] I: 27 (62.8%) C: 52 (57.8%) Quality of life Not reported Safety (adverse events and toxicity) (Grade 3-4)[d] *Nausea (N, %):* I: 2 (5.0%) C: 8 (8.9%) *Febrile neutropenial:* I: 3 (7.5%) C: 11 (12.2%)	Conclusion: Doxorubicin continues to be the standard treatment in eligible patients with advanced/metastatic soft-tissue sarcoma (STS). [c]= Overall survival was determined from the date of randomization to the date of death, whatever the cause. Patients still alive at the time of analysis were censored at the date of their last follow-up. [b]=PFS, defined as the time from random assignment until the date of either objective progression by RECIST 1.1, discontinuation of treatment or death from any cause. [a]= disease control rates (stabilisation or partial/complete responses) Response duration was determined from the time when measurement criteria were first met until the first date of objectively documented progression or death. Stable disease duration was measured in the

	declares receiving research funding from and having a consultant or advisory role with Pharmamar; and Winetter TA van der Graaf declares receiving speaker's bureau from GlaxoSmithKline and receiving research funding from GlaxoSmithKline and Novartis. All other authors declare no conflicts of interest.	multiple gated acquisition scan (MUGA), - Alkaline phosphatase =< 2.5 X ULN and albumin P 25 g/L. Additionally, - For women of childbearing potential and men the use of an effective contraception was mandatory. <u>Exclusion criteria:</u> -Patient had received any anti-cancer therapy including other systemic therapy, radiotherapy and surgery, within 28 days prior to treatment start. Additionally, main exclusion criteria included; -patients with central nervous system metastases or leptomeningeal tumor spread, - history of malignancies other than STS, -patients with in situ carcinoma of the cervix, -patients with resected incidental prostate cancer staged pT2 with Gleason score 66 and postoperative prostate-specific antigen (PSA) < 0.5 ng/ml) within the past 5 years. <u>N total at baseline:</u> 133			up at 1 month, every 6 or 12 weeks until disease progression, and every 12 weeks thereafter. <u>Loss-to-follow-up:</u> not reported <u>Intervention:</u> <u>N (%)</u> <u>Reasons (describe)</u> <u>Control:</u> <u>N (%)</u> <u>Reasons (describe)</u> <u>Incomplete outcome</u>	*Thrombocytopenia* I: 1 (2.5%) C: 14 (15.6%) *Neutropenia* I: 23 (57.5%) C: 41 (45.6%) *Fatigue* I: 2 (5.0%) C: 6 (6.7%) *Toxicity (N, %)* I: 1 (2.5%) C: 15 (16.7%)	subset of patients achieving at least stable disease, from the date of randomization until the criteria for progression were met. For patients without progression, response duration and stable disease duration were censored at the date of the last tumor assessment. [d]= The most frequent grade 3–4 AE were haematologic.

		Intervention: 43 Control T3h + T24h: 90 Important prognostic factors[2]: *For example* *Age (y): Median (range)* *I: 60 (24-77)* *C T3h: 60 (34-84)* *C T24h: 60 (23-78)* *Sex:* *I: 18 (41.9%) M* *C T3h: 18 (38.3%) M* *C T24h: 20 (46.5%)M* Groups comparable at baseline?					
Seddon (2017)	Type of study: RCT phase 3 Setting and country: Between Dec 3, 2010, and Jan 20, 2014, patients were recruited in 24 UK hospitals and one Swiss Group for Clinical Cancer Research (SAKK) hospital. Funding and conflicts of interests: The GeDDiS trial was funded by Cancer Research UK (C2921/A11561),	Inclusion criteria: -at least 13 years old (with the aim to encourage participation of the teenage and young adult population), -with histological confirmation of high-grade advanced softtissue sarcoma (defined as Trojani grade 2 or 3), measurable disease according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), -evidence of disease progression in the previous 6 months (defined as radiological progression when comparing current imaging to a previous disease assessment done	Describe intervention (treatment/procedure/test): Patients with advanced or metastatic soft-tissue sarcoma received six cycles of intravenous doxorubicin 75 mg/m² on day 1 every 3 weeks. Dose capping according to sites' local policy and dose banding to within plus or minus 5% of the calculated dose were permitted. Pre-treatment and post-treatment anti-emetics were given for all trial treatments, as per local anti-emetics policy. In both groups, patients completed up to six cycles of treatment in the absence of disease progression, intolerable side-effects, or withdrawal of consent.	Describe control (treatment/procedure/test): Patients with advanced or metastatic soft-tissue sarcoma received intravenous gemcitabine 675 mg/m² on days 1 and 8 and intravenous docetaxel 75 mg/m² on day 8 every 3 weeks. Pre-treatment and post-treatment anti-emetics were given for all trial treatments, as per local anti-emetics policy. In both groups, patients completed up to six cycles of treatment in the absence of disease progression, intolerable side-effects, or withdrawal of consent.	Length of follow-up: 24 weeks after date of randomization. Loss-to-follow-up: 3 Intervention: 1 N (%) Reasons (describe) did not start treatment after allocation to intervention group Control: 2 N (%) Reasons (describe) Did not start treatment after allocation to intervention group Incomplete outcome	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival[b] At 24 weeks: I: 86.8% (95% CI 79.6–91.6) C: 82.6% (95% CI 74.8–88.2) Progression-free survival[a] At 12 weeks: I: 72.1% [95% CI 63.5–79.0] C: 63.8% [95%CI 54.8–71.5] At 24 weeks: I: 46.3% [95% CI 37.5–54.6] C: 46.4% [95% CI 37.5–54.8]	**Comments:** -conclusion: In this randomized phase 3 trial of gemcitabine and docetaxel compared with doxorubicin as first-line therapy for locally advanced or metastatic soft-tissue sarcoma, we found no significant difference between the two treatment groups for the primary endpoint of the proportion of patients alive and progression free at 24 weeks. -registered clinical trial

	with separate funding obtained from Sarcoma UK (SUK16.2015) to support the pharmacogenomics studies described. Funding from Cancer Research UK supported the central coordination of the trial. Declaration of interests BS has received honoraria and travel grants from Novartis, Pharmamar, Ariad, Clinigen, Daiichi, and Lilly. SJS has received honoraria and travel grants from Lilly Oncology, Pharmamar, and Pfizer. PJW has received honoraria from Amgen, Bristol-Myers Squibb, Lilly, and Theradex, and research grants from AstraZeneca, Pfizer, and Virtuu. CR has received honoraria from Pfizer,	within the previous 6 months; clinical progression was accepted in patients for whom there were concerns regarding treatment delays incurred by awaiting radiological disease progression, on discussion with the chief investigator), -no previous chemotherapy for sarcoma, -no previous doxorubicin for any previously treated cancer, -WHO performance status 0–2, -a life expectancy of at least 3 months, -patients were required to have adequate organ function (absolute neutrophil count ≥1·0×10^9 per L; platelet count ≥100×10^9 per L; bilirubin ≤1·5×upper limit of normal [ULN]; aspartate transaminase, alanine transaminase, or both ≤3·0×ULN; alkaline phosphatase ≤3·0×ULN [patients were eligible with a higher alkaline phosphatase concentration if this	progression, intolerable side-effects, or withdrawal of consent.			<u>(objective) response rate[d]</u> I: 25 (19%) C: 25 (20%) <u>Quality of life [e]</u> Insufficient questionnaires were returned to be able to assess quality of life at 18 weeks and 24 weeks (83 [32%] of 257 questionnaires were returned at both 18 weeks and 24 weeks, compared with 132 [51%] of 257 at 12 weeks. <u>Safety (adverse events[c] and toxicity)</u> Grade 3-4 adverse events *Febrile neutropenia* I: 27 [17%] C: 15 [12%] *Fever* I: 18 (12%) C: 19 (15%) *Neutropenia* I: 22 (14%) C: 10 (8%)	-[a]=time from randomization to date of progression or death from any cause, whichever occurred first -[b]=time from randomization to date of death from any cause -[c]= Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The three most common serious adverse events were febrile neutropenia, fever, and neutropenia -[d]=Response was assessed by local investigators according to RECIST 1.1 (complete or partial response). -[e]=Quality of life was assessed at baseline and at 12, 18, and 24 weeks after randomization, using the EORTC QLQ-C30, and fatigue-specific FA-13 questionnaires.

	GlaxoSmithKline, Novartis, and Astellas and a research grant from Astellas. MM has received honoraria from Pharmamar and Pierre Fabre, and sponsorship for conferences from Roche and Bristol-Myers Squibb. NA has received sponsorship and funding for conferences from Pharmamar and Roche. SB has received grants from AstraZeneca and professional fees from Biocompatibles. JW, ML, FC, ZW, CB, GJV, DJ, KK, RT, SF, SN, and H-MD declare no competing interests	was shown to be due to bone isoenzyme]; measured or calculated creatinine clearance ≥30 mL/min; and cardiac ejection fraction within local normal limits), and -tumor tissue was required to be available for central review. <u>Exclusion criteria:</u> - Patients were excluded from the trial if they had alveolar soft part sarcoma, gastrointestinal stromal tumor, -Ewing's sarcoma, alveolar or embryonal rhabdomyosarcoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, dermatofibrosarcoma protuberans, malignant mixed mesodermal tumor or carcinosarcoma of the uterus, smooth muscle tumors of uncertain malignant potential of uterus, known active or uncontrolled brain metastases, active uncontrolled infection, or grade 3					

		or 4 peripheral neuropathy, -pregnant or lactating women were excluded, -patients with a history of malignancy other than sarcoma (exceptions included basal or squamous cell carcinoma of the skin and carcinoma in situ of the cervix, breast, or prostate) within 3 years before enrolment were also excluded. N total at baseline: 257 Intervention: 129 Control: 128 Important prognostic factors[2]: *For example* *Age±SD:* *I (Dox): 56 (49.4-64.0)* *C: 55 (45.6-64.0)* *Sex:* *I (DOX): 50 (39%) M* *C: 51 (40%) M* Groups comparable at baseline? yes					
Grunwald (2020)	Type of study: RCT Setting and country: Between October 2012 and march 2016, a total of 120	Inclusion criteria: - progressive advanced nonresectable or metastatic measurable disease of chemotherapy-sensitive STS subtypes in patients with local	Describe intervention (treatment/procedure/test): Elderly patients with STS. Doxorubicin was given at 75 mg/m^2 once every 3 weeks intravenously for up to 6 cycles. Dose	Describe control (treatment/procedure/test): Elderly patients with STS Pazopanib was given at 800 mg once per day until	Length of follow-up: Imaging was performed at baseline, at weeks 6, 12, 19, and 26, and every 12 weeks thereafter.	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival (12 weeks) I: 14.3 months (95% CI 8.3 to 25.9)	Comments: -conclusion: Pazopanib was noninferior to doxorubicin, rendering pazopanib a putative therapeutic option in the

	eligible patients were enrolled. <u>Funding and conflicts of interests:</u> Conflict of interest: The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I 5 Immediate Family Member, Inst 5 My Institution. Funding: sponsored by the Hanover Medical School and was executed within the academic network of the Sarcoma Working Group of the German Studies Group for Medical Oncology in cooperation with the German Interdisciplinary	histopathology and age 60 years or older. Main eligible histologies were fibrosarcoma, pleomorphic high-grade sarcoma, leiomyosarcoma, liposarcoma, alveolar or pleomorphic rhabdomyosarcoma, vascular sarcoma, synovial sarcoma not otherwise specified, and malignant peripheral nerve sheath tumors., -Adequate organ functions, -ECOG PS 0 to 2, and -availability of archived tumor tissue were additional criteria, -brain metastases were allowed if they were adequately treated, -previous anthracycline-based chemotherapy with curative intent was permitted if it had been completed more than 6 months before recurrence. <u>Exclusion criteria:</u> <u>N total at baseline: 120</u> <u>Intervention: 39</u> <u>Control: 81</u> <u>Important prognostic factors[2]:</u> <u>*For example*</u>	modifications consisted of decrements of doxorubicin to 60 mg/m. Concomitant medications were used according to local standards, and granulocyte colony-stimulating factor (G-CSF) was permitted as a prophylactic.	progression or intolerance. Dose modifications consisted of 200 mg decrements for pazopanib. Concomitant medications were used according to local standards, and granulocyte colony-stimulating factor (G-CSF) was permitted as a prophylactic.	<u>Loss-to-follow-up:</u> Missing measures at baseline were replaced by assessment on day 1 before therapy was initiated. No other imputations of data were performed. <u>Intervention:</u> <u>N (%)</u> <u>Reasons (describe)</u> <u>Control:</u> <u>N (%)</u> <u>Reasons (describe)</u> <u>Incomplete outcome</u>	C: 12.3 (95% CI 8.7 to 19.8) <u>Progression-free survival [a]</u> *12 weeks* I: 44% (95% CI 28% to 59%) C: 53% (95% CI, 42% to 64%) (P=.298) *26 weeks* I: 23% (95% CI 10% to 36%) C: 26% (95% CI 16% to 35%) (P=.738). <u>(objective) response rate[d]</u> I: 6 (15.4%) C: 10 (12.3%) <u>Quality of life [b]</u> *Global health status* I: 53.6 (45.8 to 61.4) C: 57.1 (51.7 to 62.4) <u>Safety (adverse events[c] and toxicity)</u> *Treatment-related severe adverse events* I: 10 (27.0%) C: 27 (33.3%) (p=.4933) *Any event (Grade 3-4)* I: 35 (94.6%) C: 66 (81.5%)	first-line treatment of STS in patients age 60 years or older. -clinical trial number registered -[a]= PFS defined as the time from random assignment to objective tumor progression or death as a result of any cause -[b]= using the EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (30-item) Quality of Life Questionnaire; the (EORTC QLQ-C30) was used to assess global HR-QoL in patients with cancer (not specified scale scoring). [c]= the proportion of patients with at least one severe AE. AEs were classified according to Common Terminology Criteria for Adverse Events (CTCAE 4.0). [d]= partial plus complete response rates

	Sarcoma Group and a site in Belgium	*Age (Median age, years (range)):* *I: 70 (60-81)* *C: 72 (60-88)* *Sex:* *I: 17 (43.6%) M* *C: 44 (54.3%) M* Groups comparable at baseline? Yes					
Martin-Broto (2016)	Type of study: RCT (phase 2 study) Setting and country: The study was performed within 24 Spanish centers and one Portuguese Center. Between November 2009 and October 2012, 115 patients were enrolled in the trial. Funding and conflicts of interests: Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org.	Inclusion criteria: -Patients with locally advanced nonresectable or metastatic STS; -measurable disease according to RECIST 1.0 criteria; and histologic subtypes including undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, myxofibrosarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma, angiosarcoma, epithelioid hemangioendothelioma, solitary fibrous tumors, epithelioid sarcoma, and unclassified sarcoma, -Additional criteria were Eastern Cooperative Oncologic Group performance status (ECOG PS) of 0 to 2 (category 2 was ruled out after an early amendment), -age older	Describe intervention (treatment/procedure/test): Doxorubicin was administered at 75 mg/m^2. Both schemes were administered for six cycles in the absence of progression or unacceptable toxicity.	Describe control (treatment/procedure/test): Trabectedin was administered first, because this was considered to be the most cytotoxic sequence observed in preclinical studies. Patients received trabectedin as a 3-hour infusion through a central port at 1.1 mg/m^2 , followed by doxorubicin 60 mg/m2 , administered as a 20-minute infusion. In addition to routine antiemetic, patients received intravenous dexamethasone 30 minutes before the trabectedin; 4 mg of dexamethasone was administered orally 24 and 12 hours before the trabectedin. Filgrastim was administered to all patients.	Length of follow-up: Median follow-up lengths 13 months, further not specified. Loss-to-follow-up: not reported Intervention: 3 N (%) Reasons (describe) Control: N (%) 1 Reasons (describe) Incomplete outcome	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival *Median OS:* I: 13.7 months C: 13.3 months (HR, 1.21, 95% CI, 0.77 to 1.92). Progression-free survival *At 1 year* I: 20% (95% CI, 9 to 30) C: 15% (95% CI, 5 to 25) *Median PFS* I: 5.5 months C: 5.7 months (HR 1.16, 95 % CI, 0.79 to 1.71) Partial response rate [b] *Partial response:* I: 10 (17%) C: 9 (17%) *Stable disease:* I: 27 (47%) C: 28 (53%) *Progressive disease:*	Conclusion: trabectedin plus doxorubicin did not show superiority over doxorubicin alone as first-line treatment of advanced STS. [a]= measured in accordance with the National Cancer Institute's common Terminology Criteria for Adverse Events version 3.0. [b]= tumor response according to RECIST

	The study was sponsored by the Spanish Group for Research on Sarcoma. Partially supported by Grant TRA-050, awarded by the Spanish Ministry of Health. PharmaMar Company supported shipping and expenses for clinical research organization management of the trial.	than 18 years, -and adequate bone marrow, renal, and liver function, -Normal cardiac function with left ventricular ejection fraction had to be >= 50% by echocardiogram or multigated acquisition scan (using the same method at baseline and after six cycles). Exclusion criteria: -previous chemotherapy administration, -previous radiation therapy involving the target lesions, central nervous system metastases, and- women with a positive pregnancy test. N total at baseline: 113 Intervention: 59 Control: 54 Important prognostic factors[2]: *For example* *median age, years (range):* *I: 52 (20-68)* *C: 53 (18-73)* *Sex:* *I: 30 (51% M)* *C: 32 (59% M)* Groups comparable at baseline? Yes, except for				I: 21 (36%) C: 16 (30%) Quality of life Not reported Safety (adverse events and toxicity)[a] *Grade 3 or 4 thrombocytopenia* I: 1 (2%) C: 10 (18%) *Neutropenia* I: 36 (61%) C:54 (100%) *Nausea* I: 2 (3%) C: 8 (15%) *Stomatitis;* I: 0 (0%) C: 8 (15%) *Febrile neutropenia* I: 24 (41%) C: 32 (59%)	

		some imbalances in the distribution of locally advanced tumors and leiomyosarcomas or liposarcomas which were more frequently allocated in the intervention arm.					
Judson (2014)	Type of study: RCT Setting and country: Between April 30, 2003, and May 25, 2010, at 38 hospitals in ten countries (Belgium, Canada, Denmark, France, Germany, Netherlands, Slovakia, Spain, Switzerland, UK). Funding and conflicts of interests: Funding: Cancer Research UK, EORTC Charitable Trust, UK NHS, Canadian Cancer Society Research Institute, Amgen. Declaration of interests: We have no competing interests.	Inclusion criteria: -Patients had to have histological evidence of high-grade soft-tissue sarcoma (grades 2–3) according to the Federation Nationale des Centres de Lutte Contre le Cancer grading system when applicable and radiological evidence of measurable unresectable or metastatic disease progression within 6 weeks before treatment according to RECIST (version 1.0), -patients with the following tumor types: undifferentiated pleomorphic sarcoma, myxoid or round cell liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, synovial sarcoma, myxofi bro sarcoma, fibrosarcoma, leiomyo sarcoma, angiosarcoma, malignant	Describe intervention (treatment/procedure/test): Patients with locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma. Patients assigned to receive doxorubicin alone were given doxorubicin 75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion. Treatment was repeated every 3 weeks until disease progression or unacceptable toxic effects, up to a maximum of six cycles.	Describe control (treatment/procedure/test): Patients with locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma. Those assigned to receive intensified doxorubicin and ifosfamide received doxorubicin 25 mg/m² per day on days 1–3 and ifosfamide (2·5 g/m² per day, days 1–4) plus mesna (0·5 g/m² by intravenous bolus before ifosfamide, 1·5 g/m² concurrent with ifosfamide, and 1 g/m² orally 2 h and 6 h after completion of ifosfamide infusion), followed by pegfilgrastim (6 mg subcutaneously, day 5; appendix). Treatment was repeated every 3 weeks until disease progression or unacceptable toxic eff ects, up to a maximum of six cycles.	Length of follow-up: After treatment progression, patients were followed up every 12 weeks for survival. Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival[b] *Median overall survival* I: 12.8 months (95% CI 10.5–14.3) C: 14.3 months (95% CI, 12.5-16.5 months) (HR: 0.83, 95% CI 0.67-1.03). Progression-free survival[c] *Median PFS* I: 4.6 months [95% CI 2.9–5.6] C:7.4 months [95% CI 6·6–8·3]) (HR 0.74, 95% CI 0.60–0.90). (objective) response rate[d] I: 31 (14%) C: 60 (26%) Quality of life Not reported Safety (adverse events and toxicity[a]) *Grade 3 and 4 toxic effects* *Leucopenia*	Conclusion: We found no improvement in overall survival from the administration of intensifi ed combination chemotherapy with doxorubicin plus ifosfamide compared with doxorubicin alone. [a]=side-effects of treatment were graded according to International Common Toxicity Criteria. [b]=Overall survival was computed from the date of randomization to the date of death from any cause. Patients alive at the time of the analysis were censored at their last follow-up date. [c]= Progression-free survival was computed from the date of randomization to the first

		peripheral nerve sheath tumor, epithelioid sarcoma, unclassified high-grade sarcoma (not otherwise specified) were included, -patients had to be age 18–60 years, -patients had to have a WHO performance status of 0 or 1, -absolute neutrophil count more than 2×10^9 cells per L, - more than 100×10^9 platelets per L, serum creatinine of 120 µmol/L or less or calculated creatinine clearance (Cockroft and Gault method) more than 65 mL/min, - patients had to have two functioning kidneys, bilirubin 30 µmol/L or less, and albumin more than 25 g/L, -patients also had to have a normal (according to local assessments) left ventricular ejection fraction by multiple gated acquisition scan or echocardiogram, - women of child-bearing potential had to take adequate contraceptive measures and have a negative pregnancy test within 7 days of study entry. <u>Exclusion criteria:</u>				I: 40 (18%) C: 97 (43%) *Neutropenia* I: 83 (37%) C: 93 (42%) *Febrile neutropenia* I: 30 (13%) C: 103 (46%) *Anaemia* I: 10 (4%) C: 78 (35%) *Thrombocytopenia* I: 1 (<1%) C: 75 (33%)	recorded date of progression or death. Patients alive and progression-free at the time of analysis were censored at the date of last follow-up. [d]= complete plus partial responses

		Patients with - gastrointestinal stromal tumor, mixed mesodermal tumor, chondrosarcoma, malignant mesothelioma, neuroblastoma, osteosarcoma, Ewing's sarcoma, desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, and alveolar soft part sarcoma were excluded, also having other severe illness (eg, psychosis or previous history of cardiovascular disease), symptomatic or known CNS metastases, previous or concurrent second primary malignant tumors (except adequately treated insitu carcinoma of cervix or basal cell carcinoma) was an exclusion criteria, - patients who had had radiotherapy to the sole available index lesion or those who had received chemotherapy for advanced disease, although previous adjuvant chemotherapy (preoperative or postoperative) was allowed if disease progression had not occurred within 6 months of completion.					

		N total at baseline: 455 Intervention: 228 Control: 227 Important prognostic factors[2]: *For example* *Age (Median (IQR; years);* *I:* 48 (41-55) *C:* 47 (39-54) *Sex:* *I:* 103 (45%M) *C:* 114 (505M) Groups comparable at baseline? yes					

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Pautier (2022)	Definitely yes; <u>Reason:</u> Investigators identified and enrolled the patients into the trial. Patients were randomly assigned (1:1) into the doxorubicin alone group or the doxorubicin plus	Probably yes; <u>Reason:</u> The random assignment request was signed by the investigator and sent by fax to the data center. The data manager randomly assigned each patient using the online	Probably yes; <u>Reason:</u> Randomization and analysis of data blinded: the tumor response was assessed by the investigator using RECIST version 1.1 (using thoracic and abdominalpelvic	Probably yes; <u>Reason:</u> Efficacy analyses were performed on all randomly assigned patients, based on the intention-to-treat principle.	Definitely yes; <u>Reason:</u> All relevant outcomes were reported;	Probably yes; <u>Reason:</u> Funding: PharmaMar.	<u>overall survival</u> **Low concerns of bias** <u>progression free survival</u> **Low concerns of bias** <u>response rate</u> **Low concerns of bias** <u>quality of life</u> not reported

	trabectedin group by means of an interactive web response system. Random assignment was stratified by tumor location (uterus vs soft tissue) and disease (locally advanced vs metastatic). Permuted blocks of different sizes (from two to six) were used to allocate the patients to each treatment group.	TENALEA randomization software version 2.2. A report with each randomization number and a group assignment was then provided to the investigator. Because of the open-label trial design, the patients, investigators, and the study sponsor were not masked to the study treatment.	CT scans or MRI). For the primary endpoint analysis (progression-free survival), a blinded radiographic central review, based on imaging only (using thoracic and abdominal-pelvic CT scans or MRI), was performed at the Gustave-Roussy hospital (before the database was locked, ie, no further data were added) to confirm progression. The primary endpoint was progression-free survival assessed by blinded independent central review and according to Response Evaluation Criteria in Solid Tumors 1.1 criteria. Patients, health care providers; blinding not reported				<u>safety</u> *adverse events* **Low concerns of bias** *toxicity* **Low concerns of bias**
Bui-Nguyen (2015)	Probably yes; <u>Reason:</u> Parallel assignment to the treatment groups. Eligible patients were randomized in a 1:1:1 ratio: (two intervention groups and one control). The randomization was stratified by institution,	Definitely no; <u>Reason:</u> Allocation sequence not specified/reported.	Probably no; <u>Reason:</u> Open label study; thus no masking/blinding. Perhaps data analysts were blinded; ''*The results of the planned interim analysis at the end of the first step*	Definitely no; <u>Reason:</u> Not reported.	Probably yes; <u>Reason:</u> Quality of life assessment was reported in study protocol, however findings regarding QOL not reported in this study (Bui-Nguyen, 2015).	Probably no; <u>Reason:</u> Results of step 1: none of the experimental arms fulfils expectations and the study will not continue as a phase III.	<u>Overall survival</u> **High concerns of risk** <u>PFS</u> **High concerns of risk** <u>Response rate</u> **High concerns of risk** <u>QOL</u> **Not reported**

	age at registration (</>=60 years) and presence of liver metastases (no/yes).		*were reviewed by an independent data monitoring committee on 4th July 2013''*. May be assumed that patients were not aware about the type of chemotherapy they received, however unsure (not reported). ''*All infusions were administered with a central venous catheter*'', and ''*The use of growth factors was left to the discretion of the investigator*''.				Adverse events **High concerns of risk**
Seddon (2017)	Probably yes; Reason: Patients were randomly allocated in a 1:1 ratio to receive either gemcitabine and docetaxel or doxorubicin. Patients were stratified by age (≤18 years vs >18 years) and histological subtype (uterine leiomyosarcoma vs synovial sarcoma vs pleomorphic sarcoma vs other eligible sarcomas). We chose these specific histological strata on the basis of available	Probably yes; Reason: Treatment was assigned centrally by computer at the Cancer Research UK and University College London Cancer Trials Centre (UCL CTC; London, UK) using a minimisation algorithm incorporating a random element. Treatment allocation was communicated electronically to the site randomizing the patient. Treatment allocation was not masked	Probably no; Reason: Not reported. Solely stated that all pathology samples were reviewed by a single histopathologist (RT) (before randomization). During trial, not reported whom was blinded.	Probably yes; Reason: ITT performed, solely for outcome measure adverse events – solely those patients who received at least one dose of their randomly assigned treatment (n=254) were analysed. Three were excluded due to not receiving the intervention/control.	Probably no; Reason: Regarding outcome measure quality of life ''*Insufficient questionnaires were returned to be able to assess quality of life at 18 weeks and 24 weeks (83 [32%] of 257 questionnaires were returned at both 18 weeks and 24 weeks, compared with 132 [51%] of 257 at 12 weeks*.''	Probably yes; /	Overall survival **Some concerns of risk** PFS **Some concerns of risk** Response rate **Some concerns of risk** QOL **Not reported** Adverse events **Some concerns of risk**

	evidence at the time of trial design suggesting potential differential disease response to chemotherapy in the different strata.						
Grunwald (2020)	Probably yes; <u>Reason:</u> A randomization list was prepared before the study for permuted blocks of variable sizes and a 2:1 randomization ratio for comparing pazopanib and doxorubicin. Randomization was stratified by ECOG PS of 0 to 1 versus 2 and liposarcoma histology.	Definitely no; <u>Reason:</u> Concealment of allocation not reported.	Probably no; <u>Reason:</u> Blinding not reported.	Probably no; <u>Reason:</u> Loss to follow-up not reported.	Definitely yes; <u>Reason:</u> All relevant outcomes were reported	Probably no; <u>Reason:</u>	<u>Overall survival</u> **High concerns of risk** <u>PFS:</u> **High concerns of risk** <u>Response rate</u> **High concerns of risk** <u>QOL</u> **High concerns of risk** <u>Adverse events</u> **High concerns of risk**
Martin-Broto (2016)	Probably yes; <u>Reason:</u> Patients were stratified according to metastatic disease-free interval (=< 12 months or > 12 months). Patients were randomly assigned to each arm, and central pathologic review was planned for all patients.	Definitely no; <u>Reason:</u> Concealment of allocation not reported.	Probably no; <u>Reason:</u> Not reported, solely stated that ''*The participants were blindly assessed by an expert pathologist in the field of sarcoma (R.R.) for both diagnostic confirmation and translational purposes.*''	Probably no; <u>Reason:</u> Loss to follow-up small (n=3 and n=1 in respectively the intervention and control group).	Definitely yes; <u>Reason:</u> All relevant outcomes were reported;	Probably yes; <u>Reason:</u> PharmaMar Company supported shipping and expenses for clinical research organization management of the trial.	<u>Overall survival</u> **High concerns of risk** <u>PFS:</u> **High concerns of risk** <u>Response rate</u> **High concerns of risk** <u>QOL</u> **Not reported** <u>Adverse events</u> **High concerns of risk**
Judson (2014)	Definitely yes; <u>Reason:</u>	Probably no; <u>Reason:</u> Allocation sequence not reported, solely	Probably no; <u>Reason:</u> Not reported	Probably no; <u>Reason:</u> Eight patients did not start treatment and	Definitely yes; Reason: All relevant outcomes were reported;	Probably no;	<u>Overall survival</u> **Some concerns of risk** <u>PFS:</u> **Some concerns of risk**

	The randomization sequence was generated by an online randomized trial access system based on the minimisation method. Randomization was stratified by center, performance status (0 vs 1), age (<50 years vs ≥50 years), liver metastases (present vs absent), and histological grade (2 vs 3).	stated that ''*A panel of specialist sarcoma pathologists did a mandatory central pathology review but patients were enrolled on the basis of local diagnosis*.'' And '' *Neither patients nor investigators were masked to treatment allocation*.''.		three did not receive the allocated treatment (figure 1). As a result, the safety population consisted of 447 patients and the per-protocol population of 432 patients.			<u>Response rate</u> **Some concerns of risk** <u>QOL</u> **Not reported** <u>Adverse events</u> **Some concerns of risk**

Table of excluded studies

Reference	Reason for exclusion
Ben-Ami, E. and Hornick, J. L. and Wagner, A. J. The potential of emerging new therapeutics for the treatment of perivascular epithelioid cell tumors (PEComa). Expert Opinion on Orphan Drugs. 2018; 6 (9) :537-543	The only prospective clinical trial for advanced PEComa is the phase 2 study of ABI-009, a nanoparticle albumin-bound mTOR inhibitor. Yet this has wrong study design since it is a single-arm study (NCT0249457)
Blay, J. Y. and Schoffski, P. and Bauer, S. and Krarup-Hansen, A. and Benson, C. and D'Adamo, D. R. and Guo, M. and Maki, R. Subgroup analysis of leiomyosarcoma (LMS) patients (pts) from a phase 3, open-label, randomized study of eribulin (ERI) versus dacarbazine (DTIC) in pts with advanced liposarcoma (LPS) and LMS. Annals of Oncology. 2016; 27 :vi485	Not first line
Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, Khamly K, Ganjoo K, Nagarkar R, Wieland S, Levitt DJ. First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized Clinical Trial. JAMA Oncol. 2015 Dec;1(9):1272-80. doi: 10.1001/jamaoncol.2015.3101. PMID: 26378637.	Wrong intervention: drug not available in NL
D'Angelo, S. P. and Mahoney, M. R. and Van Tine, B. A. and Atkins, J. and Milhem, M. M. and Jahagirdar, B. N. and Antonescu, C. R. and Horvath, E. and Tap, W. D. and Schwartz, G. K. and Streicher, H. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. The Lancet Oncology. 2018; 19 (3) :416-426	Not first line
Desar IME, Ottevanger PB, Benson C, van der Graaf WTA. Systemic treatment in adult uterine sarcomas. Crit Rev Oncol Hematol. 2018 Feb;122:10-20. doi: 10.1016/j.critrevonc.2017.12.009. Epub 2017 Dec 14. PMID: 29458779.	The relevant RCTs (>2015) in this SR are already included in this literature search (Seddon et al., 2017; Tap et al., 2016; Martin-Broto et al., 2016; Hensley et al., 2015; Judson et al., 2014)
Dickson MA, D'Adamo DR, Keohan ML, D'Angelo SP, Carvajal RD, Gounder MM, Maki RG, Qin LX, Lefkowitz RA, McKennon OR, Hirst CM, Schwartz GK, Tap WD. Phase II Trial of Gemcitabine and Docetaxel with Bevacizumab in Soft Tissue Sarcoma. Sarcoma. 2015;2015:532478. doi: 10.1155/2015/532478. Epub 2015 May 14. PMID: 26074722; PMCID: PMC4446476.	Single arm,wrong study design
Duffaud F, Maki RG, Jones RL. Treatment of advanced soft tissue sarcoma: efficacy and safety of trabectedin, a multitarget agent, and update on other systemic therapeutic options. Expert Rev Clin Pharmacol. 2016 Apr;9(4):501-512. doi: 10.1586/17512433.2016.1152179. PMID: 26873304.	No comparison of two intervention(s)
Garcia del Muro X, de Alava E, Artigas V, Bague S, Braña A, Cubedo R, Cruz J, Mulet-Margalef N, Narvaez JA, Martinez Tirado O, Valverde C, Verges R, Viñals J, Martin-Broto J; Spanish Group for Research on Sarcoma. Clinical practice guidelines for the diagnosis and treatment of patients with soft tissue sarcoma by the Spanish group for research in sarcomas (GEIS). Cancer Chemother Pharmacol. 2016 Jan;77(1):133-46. doi: 10.1007/s00280-015-2809-5. Epub 2015 Nov 12. PMID: 26563256; PMCID: PMC4706580.	Wrong study design: no SR or RCT
Gounder, Mrinal and Schoffski, Patrick and Jones, Robin L. and Agulnik, Mark and Cote, Gregory M. and Villalobos, Victor M. and Attia, Steven and Chugh, Rashmi and Chen, Tom Wei-Wu and Jahan, Thierry and Loggers, Elizabeth T. and Gupta, Abha and Italiano, Antoine and Demetri, George D. and Ratan, Ravin and Davis, Lara E. and Mir, Olivier and Dileo, Palma and Van Tine, Brian A. and Pressey, Joseph G. and Lingaraj, Trupti and Rajarethinam, Anand and Sierra, Laura and Agarwal, Shefali and Stacchiotti, Silvia Tazemetostat in advanced epithelioid sarcoma	No comparison of intervention(s), solely the clinical activity and safety of tazemetostat was studied

with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. The Lancet. Oncology. 2020; 21 (11) :1423-1432	
Hartmann JT, Kopp HG, Gruenwald V, Piperno-Neumann S, Kunitz A, Hofheinz R, Mueller L, Geissler M, Horger M, Fix P, Chemnitz JM, Neise M, Wehler T, Zander I, Eckert R, Hann von Weyhern C, Bauer S, Mayer F; German Sarcoma Group within the Working Group Medical Oncology (AIO) of the German Cancer Society/AIO-STS-002, Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft e.V. Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma. Eur J Cancer. 2020 Jan;124:152-160. doi: 10.1016/j.ejca.2019.10.016. Epub 2019 Nov 28. PMID: 31785463.	trofosfamide not available
Hensley ML, Miller A, O'Malley DM, Mannel RS, Behbakht K, Bakkum-Gamez JN, Michael H. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol. 2015 Apr 1;33(10):1180-5. doi: 10.1200/JCO.2014.58.3781. Epub 2015 Feb 23. PMID: 25713428; PMCID: PMC4372854.	Wrong comparison (no comparison with doxocubicin)
Hentschel, L. and Richter, S. and Kopp, H. G. and Kasper, B. and Kunitz, A. and Grünwald, V. and Kessler, T. and Chemnitz, J. M. and Pelzer, U. and Schuler, U. and Freitag, J. and Schilling, A. and Hornemann, B. and Arndt, K. and Bornhäuser, M. and Schuler, M. K. Quality of life and added value of a tailored palliative care intervention in patients with soft tissue sarcoma undergoing treatment with trabectedin: a multicentre, cluster-randomised trial within the German Interdisciplinary Sarcoma Group (GISG). BMJ open. 2020; 10 (8) :e035546	No comparison between interventions, solely studied outcomes related to treatment with ''trabectedin''. Patients could be included in a control arm (CA)
Jones, R. L. and Chawla, S. P. and Attia, S. and Schöffski, P. and Gelderblom, H. and Chmielowski, B. and Le Cesne, A. and Van Tine, B. A. and Trent, J. C. and Patel, S. and Wagner, A. J. and Chugh, R. and Heyburn, J. W. and Weil, S. C. and Wang, W. and Viele, K. and Maki, R. G. A phase 1 and randomized controlled phase 2 trial of the safety and efficacy of the combination of gemcitabine and docetaxel with ontuxizumab (MORAb-004) in metastatic soft-tissue sarcomas. Cancer. 2019; 125 (14) :2445-2454	no interventions compared: comparison is ontuxizumab vs placebo
Judson, I. and Morden, J. P. and Kilburn, L. and Leahy, M. and Benson, C. and Bhadri, V. and Campbell-Hewson, Q. and Cubedo, R. and Dangoor, A. and Fox, L. and Hennig, I. and Jarman, K. and Joubert, W. and Kernaghan, S. and López Pousa, A. and McNeil, C. and Seddon, B. and Snowdon, C. and Tattersall, M. and Toms, C. and Martinez Trufero, J. and Bliss, J. M. Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. The Lancet Oncology. 2019; 20 (7) :1023-1034	Not first line
Karch A, Koch A, Grünwald V. A phase II trial comparing pazopanib with doxorubicin as first-line treatment in elderly patients with metastatic or advanced soft tissue sarcoma (EPAZ): study protocol for a randomized controlled trial. Trials. 2016 Jul 7;17(1):312. doi: 10.1186/s13063-016-1434-x. PMID: 27387325; PMCID: PMC4936293.	Wrong study design: no SR or RCT
Kotecki N, Le Cesne A, Tresch-Bruneel E, Ray-Coquard I, Chevreau C, Bertucci F, Bogart E, Mir O, Pautier P, Decoupigny E, Clisant S, Blay JY, Penel N. Impact of Trabectedin Interruption and Subsequent Rechallenge on Progression in Patients With Advanced Soft Tissue Sarcoma: Long-term Follow-up of the T-DIS trial. Am J Clin Oncol. 2018 Nov;41(11):1094-1100. doi: 10.1097/COC.0000000000000430. PMID: 29509592.	No comparison between interventions: the impact of trabectedin discontinuation after subsequent rechallenge was studied (number of cycles trabectedin provided).
Krown, S. E. and Moser, C. B. and MacPhail, P. and Matining, R. M. and Godfrey, C. and Caruso, S. R. and Hosseinipour, M. C. and Samaneka, W. and Nyirenda, M. and Busakhala, N. W. and Okuku,	Does not meet the P in PICO: patients with AIDS-associated Kaposi sarcomanon were studied

F. M. and Kosgei, J. and Hoagland, B. and Mwelase, N. and Oliver, V. O. and Burger, H. and Mngqibisa, R. and Nokta, M. and Campbell, T. B. and Borok, M. Z. and Moses, A. and Kanyama, C. and Mukwekwerere, P. and Gudza, I. and Chauwa, F. and Ulaya, G. and Kutto, I. and Cheruiyot, P. and Okello, C. and Nakaganda, A. and Koskei, G. and Keter, W. and Netto, J. and Baião, T. and Govender, I. and O'Connell-Maritz, J. and Cain, K. and Okanda, J. and Cornelissen, L. and Van Schalkwyk, M. and Sikhosana, R. and Ngcobo, M. and Lee, J. Y. and Harrison, T. and Wachsman, W. and Shin, K. and Evans, S. and Rothenberg, J. and Hosey, L. and McCarthy, S. and Martinez-Maza, O. and Rinaldo, C. and Dittmer, D. and Fletcher, C. and Rudek, M. and Asmelash, A. and Hughes, V. and Schouten, J. and Shugarts, D. and Kujinga, T. and Zadzilka, A. and Kerui, F. and Robertson, D. and Rooney, J. and Sewal, K. and Gottshall, B. Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial. The Lancet. 2020; 395 (10231) :1195-1207	
Liu, J. and Fan, Z. and Li, S. and Xue, R. and Gao, T. and Bai, C. and Zhang, L. and Tan, Z. and Fang, Z. Anlotinib hydrochloride capsules for advanced soft tissue sarcoma: Single-center data analysis of a stage II multicenter clinical trial. Chinese Journal of Clinical Oncology. 2018; 45 (20) :1066-1070	No comparison between interventions, solely intervention (anlotinib capsules) was compared to placebo
Martin E, Lamba N, Flucke UE, Verhoef C, Coert JH, Versleijen-Jonkers YMH, Desar IME. Non-cytotoxic systemic treatment in malignant peripheral nerve sheath tumors (MPNST): A systematic review from bench to bedside. Crit Rev Oncol Hematol. 2019 Jun;138:223-232. doi: 10.1016/j.critrevonc.2019.04.007. Epub 2019 Apr 19. PMID: 31092379.	Interventions are immune therapies (e.g. oncolytic viruses)
Navarrete-Dechent C, Mori S, Barker CA, Dickson MA, Nehal KS. Imatinib Treatment for Locally Advanced or Metastatic Dermatofibrosarcoma Protuberans: A Systematic Review. JAMA Dermatol. 2019 Mar 1;155(3):361-369. doi: 10.1001/jamadermatol.2018.4940. PMID: 30601909; PMCID: PMC8909640.	The few studies that refered to metastatic cases did not compare two interventions and solely studied a.o. one intervention: imatinib mesylate), or the therapeutic activity and safety of imatinib.
Nguyen J, Takebe N, Kummar S, Razak A, Chawla SP, George S, Patel SR, Keohan ML, Movva S, O'Sullivan Coyne G, Do K, Juwara L, Augustine B, Steinberg SM, Kuhlmann L, Ivy SP, Doroshow JH, Chen AP. Randomized Phase II Trial of Sunitinib or Cediranib in Alveolar Soft Part Sarcoma. Clin Cancer Res. 2023 Apr 3;29(7):1200-1208. doi: 10.1158/1078-0432.CCR-22-2145. PMID: 36302173; PMCID: PMC10068440.	Not first line
Otake A, Matsuzaki S, Ueda Y, Yoshino K. Chapter: Chemotherapy for uterine sarcomas: A review. Front. Drug Des. and Discov. 2016; 7 :139-151	Book chapter, wrong study design
Paoluzzi L, Maki RG. Diagnosis, Prognosis, and Treatment of Alveolar Soft-Part Sarcoma: A Review. JAMA Oncol. 2019 Feb 1;5(2):254-260. doi: 10.1001/jamaoncol.2018.4490. PMID: 30347044.	No chemotherapy intervention(s) compared
Pautier P, Floquet A, Chevreau C, Penel N, Guillemet C, Delcambre C, Cupissol D, Selle F, Isambert N, Piperno-Neumann S, Saada-Bouzid E, Bertucci F, Bompas E, Alexandre J, Collard O, Lebrun-Ly V, Soulier P, Toulmonde M, Le Cesne A, Lacas B, Duffaud F; French Sarcoma Group. A single-arm multicentre phase II trial of doxorubicin in combination with trabectedin in the first-line treatment for leiomyosarcoma with long-term follow-up and impact of cytoreductive surgery. ESMO Open. 2021 Aug;6(4):100209. doi: 10.1016/j.esmoop.2021.100209. Epub 2021 Jul 26. PMID: 34325109; PMCID: PMC8446791.	Single arm, wrong study design
Pink D, Andreou D, Bauer S, Brodowicz T, Kasper B, Reichardt P, Richter S, Lindner LH, Szkandera J, Grünwald V, Kebenko M, Kirchner M, Hohenberger P. Treatment of Angiosarcoma with Pazopanib and Paclitaxel: Results of the EVA (Evaluation of	No comparison between interventions, study is an evaluation study of efficacy and toxicity of paclitaxel + pazopanib

Votrient® in Angiosarcoma) Phase II Trial of the German Interdisciplinary Sarcoma Group (GISG-06). Cancers (Basel). 2021 Mar 11;13(6):1223. doi: 10.3390/cancers13061223. PMID: 33799576; PMCID: PMC8000466.	
Ray-Coquard I, Rizzo E, Blay JY, Casali P, Judson I, Hansen AK, Lindner LH, Dei Tos AP, Gelderblom H, Marreaud S, Litière S, Rutkowski P, Hohenberger P, Gronchi A, van der Graaf WT. Impact of chemotherapy in uterine sarcoma (UtS): review of 13 clinical trials from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) involving advanced/metastatic UtS compared to other soft tissue sarcoma (STS) patients treated with first line chemotherapy. Gynecol Oncol. 2016 Jul;142(1):95-101. doi: 10.1016/j.ygyno.2016.05.016. Epub 2016 May 24. PMID: 27208537.	<2015. Review used pooled data of patients registered in EORTC-STBSG sarcoma trials from 1977 to 2010
Riedel RF, Jones RL, Italiano A, Bohac C, Thompson JC, Mueller K, Khan Z, Pollack SM, Van Tine BA. Systemic Anti-Cancer Therapy in Synovial Sarcoma: A Systematic Review. Cancers (Basel). 2018 Nov 1;10(11):417. doi: 10.3390/cancers10110417. PMID: 30388821; PMCID: PMC6267101.	No first line intervention(s) compared
Ryan CW, Merimsky O, Agulnik M, Blay JY, Schuetze SM, Van Tine BA, Jones RL, Elias AD, Choy E, Alcindor T, Keedy VL, Reed DR, Taub RN, Italiano A, Garcia Del Muro X, Judson IR, Buck JY, Lebel F, Lewis JJ, Maki RG, Schöffski P. PICASSO III: A Phase III, Placebo-Controlled Study of Doxorubicin With or Without Palifosfamide in Patients With Metastatic Soft Tissue Sarcoma. J Clin Oncol. 2016 Nov 10;34(32):3898-3905. doi: 10.1200/JCO.2016.67.6684. Epub 2016 Sep 30. PMID: 27621408.	Intervention not available
Saerens M, Brusselaers N, Rottey S, Decruyenaere A, Creytens D, Lapeire L. Immune checkpoint inhibitors in treatment of soft-tissue sarcoma: A systematic review and meta-analysis. Eur J Cancer. 2021 Jul;152:165-182. doi: 10.1016/j.ejca.2021.04.034. Epub 2021 Jun 6. PMID: 34107450.	Not first line: review assessed immune checkpoint inhibitors which can be considered Immunotherapy drugs
Saiag P, Grob JJ, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, Peris K, Stratigos A, Middelton M, Basholt L, Testori A, Garbe C. Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline. Eur J Cancer. 2015 Nov;51(17):2604-8. doi: 10.1016/j.ejca.2015.06.108. Epub 2015 Jul 16. PMID: 26189684.	Wrong study design: no SR or RCT
Schoot RA, Chisholm JC, Casanova M, Minard-Colin V, Geoerger B, Cameron AL, Coppadoro B, Zanetti I, Orbach D, Kelsey A, Rogers T, Guizani C, Elze M, Ben-Arush M, McHugh K, van Rijn RR, Ferman S, Gallego S, Ferrari A, Jenney M, Bisogno G, Merks JHM. Metastatic Rhabdomyosarcoma: Results of the European Paediatric Soft Tissue Sarcoma Study Group MTS 2008 Study and Pooled Analysis With the Concurrent BERNIE Study. J Clin Oncol. 2022 Nov 10;40(32):3730-3740. doi: 10.1200/JCO.21.02981. Epub 2022 Jun 16. PMID: 35709412; PMCID: PMC9649279.	<2015. MTS conducted before 2008, and Bernie conducted from 2008 to 2013
Tanaka K, Kawano M, Iwasaki T, Itonaga I, Tsumura H. A meta-analysis of randomized controlled trials that compare standard doxorubicin with other first-line chemotherapies for advanced/metastatic soft tissue sarcomas. PLoS One. 2019 Jan 10;14(1):e0210671. doi: 10.1371/journal.pone.0210671. PMID: 30629708; PMCID: PMC6328231.	<2015: meta-analysis included RCTs which were published between january 1974 and september 2018. The RCTs >2015 were already listed in this literature review: Chawla, 2015; Bui-Nguyen 2015; Martin-Broto 2016; Seddon 2017; Tap, 2016; and Tap 2017
Tap W, Papai Z, Van Tine B, Attia S, Ganjoo K, Jones RL, Schoffski P. Randomized phase 3, multicenter, open-label study comparing evofosfamide (Evo) in combination with doxorubicin (D) vs. D alone in patients (pts) with advanced soft tissue sarcoma (STS): Study TH-CR-406/SARC021. Annals of Oncology, 27, vi483. 2016. doi: 10.1093/annonc/mdw388.01.	Drugs not available
Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, Schuetze S, Reed D, Chawla SP, Riedel RF, Krarup-Hansen A, Toulmonde M, Ray-Coquard I, Hohenberger P, Grignani G,	An updated version of this article is already included in our literature search (''Correction to Doxorubicin plus

Cranmer LD, Okuno S, Agulnik M, Read W, Ryan CW, Alcindor T, Del Muro XFG, Budd GT, Tawbi H, Pearce T, Kroll S, Reinke DK, Schöffski P. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2017 Aug;18(8):1089-1103. doi: 10.1016/S1470-2045(17)30381-9. Epub 2017 Jun 23. Erratum in: Lancet Oncol. 2018 Feb;19(2):e78. PMID: 28651927; PMCID: PMC7771354.	evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial (Lancet Oncol (2017) 18 (1089–103)(S1470204517303819), (10.1016/S1470-2045(17)30381-9))''
Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, Agulnik M, Cooney MM, Livingston MB, Pennock G, Hameed MR, Shah GD, Qin A, Shahir A, Cronier DM, Ilaria R Jr, Conti I, Cosaert J, Schwartz GK. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016 Jul 30;388(10043):488-97. doi: 10.1016/S0140-6736(16)30587-6. Epub 2016 Jun 9. Erratum in: Lancet. 2016 Jul 30;388(10043):464. PMID: 27291997; PMCID: PMC5647653.	Wrong intervention: drug not available in NL
Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, Schuetze S, Reed D, Chawla SP, Riedel RF, Krarup-Hansen A, Toulmonde M, Ray-Coquard I, Hohenberger P, Grignani G, Cranmer LD, Okuno S, Agulnik M, Read W, Ryan CW, Alcindor T, Del Muro XFG, Budd GT, Tawbi H, Pearce T, Kroll S, Reinke DK, Schöffski P. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2017 Aug;18(8):1089-1103. doi: 10.1016/S1470-2045(17)30381-9. Epub 2017 Jun 23. Erratum in: Lancet Oncol. 2018 Feb;19(2):e78. PMID: 28651927; PMCID: PMC7771354.	Wrong intervention: drug not available in NL
Tap WD, Wagner AJ, Schöffski P, Martin-Broto J, Krarup-Hansen A, Ganjoo KN, Yen CC, Abdul Razak AR, Spira A, Kawai A, Le Cesne A, Van Tine BA, Naito Y, Park SH, Fedenko A, Pápai Z, Soldatenkova V, Shahir A, Mo G, Wright J, Jones RL; ANNOUNCE Investigators. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. JAMA. 2020 Apr 7;323(13):1266-1276. doi: 10.1001/jama.2020.1707. PMID: 32259228; PMCID: PMC7139275.	Wrong intervention: drug not available in NL
Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). Electronic address: andrea.macneill@bccancer.bc.ca. Management of metastatic retroperitoneal sarcoma: a consensus approach from the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). Ann Oncol. 2018 Apr 1;29(4):857-871. doi: 10.1093/annonc/mdy052. PMID: 29432564; PMCID: PMC6354678.	Wrong study design: no SR or RCT
Tsakatikas S, Papageorgiou G, Fioretzaki R, Kosmas C. An overview of current results with the vincristine-irinotecan-temozolomide combination with or without bevacizumab in pediatric, adolescence and adult solid tumors. Crit Rev Oncol Hematol. 2021 Oct;166:103457. doi: 10.1016/j.critrevonc.2021.103457. Epub 2021 Aug 21. PMID: 34428555.	Not referred to rhabdomyosarcoom
Van Tine BA, Hirbe AC, Oppelt P, Frith AE, Rathore R, Mitchell JD, Wan F, Berry S, Landeau M, Heberton GA, Gorcsan J 3rd, Huntjens PR, Soyama Y, Vader JM, Alvarez-Cardona JA, Zhang KW, Lenihan DJ, Krone RJ. Interim Analysis of the Phase II Study: Noninferiority Study of Doxorubicin with Upfront Dexrazoxane plus Olaratumab for Advanced or Metastatic Soft-Tissue Sarcoma. Clin Cancer Res. 2021 Jul 15;27(14):3854-3860. doi: 10.1158/1078-0432.CCR-20-4621. Epub 2021 Mar 25. PMID: 33766818; PMCID: PMC8282681.	Wrong study design.
Verma S, Kalra K, Rastogi S, Dhamija E, Upadhyay A, Mittal A, Aggarwal A, Shamim SA. Trabectedin in Advanced Sarcomas-Experience at a Tertiary Care Center and Review of Literature.	Study solely assessed the dosage of one intervention (trabectedin)

South Asian J Cancer. 2021 Apr;10(2):53-57. doi: 10.1055/s-0041-1734336. Epub 2021 Sep 23. PMID: 34568214; PMCID: PMC8460345.	
Verschoor AJ, Litière S, Marréaud S, Judson I, Toulmonde M, Wardelmann E, LeCesne A, Gelderblom H. Survival of soft tissue sarcoma patients after completing six cycles of first-line anthracycline containing treatment: an EORTC-STBSG database study. Clin Sarcoma Res. 2020 Sep 9;10:18. doi: 10.1186/s13569-020-00137-5. PMID: 32944214; PMCID: PMC7488114.	Wrong study design: no SR or RCT
Vlenterie M, Litière S, Rizzo E, Marréaud S, Judson I, Gelderblom H, Le Cesne A, Wardelmann E, Messiou C, Gronchi A, van der Graaf WT. Outcome of chemotherapy in advanced synovial sarcoma patients: Review of 15 clinical trials from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group; setting a new landmark for studies in this entity. Eur J Cancer. 2016 May;58:62-72. doi: 10.1016/j.ejca.2016.02.002. Epub 2016 Mar 8. PMID: 26968015.	No intervention(s) compared.
Wang BC, Kuang BH, Xiao BY, Lin GH. Doxorubicin/Adriamycin Monotherapy or Plus Ifosfamide in First-Line Treatment for Advanced Soft Tissue Sarcoma: A Pooled Analysis of Randomized Trials. Front Oncol. 2021 Nov 22;11:762288. doi: 10.3389/fonc.2021.762288. PMID: 34881180; PMCID: PMC8648074.	No description relevant studies and no risk of bias tables studies presented.
Wilky, B. A. and Trucco, M. M. and Subhawong, T. K. and Florou, V. and Park, W. and Kwon, D. and Wieder, E. D. and Kolonias, D. and Rosenberg, A. E. and Kerr, D. A. and Sfakianaki, E. and Foley, M. and Merchan, J. R. and Komanduri, K. V. and Trent, J. C. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. The Lancet Oncology. 2019; 20 (6) :837-848	Not first line
Young RJ, Litière S, Lia M, Hogendoorn PCW, Fisher C, Mechtersheimer G, Daugaard S, Sciot R, Collin F, Messiou C, Grünwald V, Gronchi A, van der Graaf W, Wardelmann E, Judson I. Predictive and prognostic factors associated with soft tissue sarcoma response to chemotherapy: a subgroup analysis of the European Organisation for Research and Treatment of Cancer 62012 study. Acta Oncol. 2017 Jul;56(7):1013-1020. doi: 10.1080/0284186X.2017.1315173. Epub 2017 Apr 21. PMID: 28431480.	Orignal article (which is suggested to include in literature search) is: ''Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15:415–423.''
Younger, E. and Ballman, K. and Lu, Y. and Pápai, Z. and Van Tine, B. A. and Attia, S. and Schöffski, P. and Reinke, D. and Tap, W. D. and Jones, R. L. Subgroup analysis of older patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide (SARC021) trial. Journal of Geriatric Oncology. 2020; 11 (3) :463-469	Subgroup analyses; original study is included in literature search (Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial)
Younger, E. and Litière, S. and Le Cesne, A. and Mir, O. and Gelderblom, H. and Italiano, A. and Marreaud, S. and Jones, R. L. and Gronchi, A. and van der Graaf, W. T. A. Outcomes of Elderly Patients with Advanced Soft Tissue Sarcoma Treated with First-Line Chemotherapy: A Pooled Analysis of 12 EORTC Soft Tissue and Bone Sarcoma Group Trials. Oncologist. 2018; 23 (10) :1250-1259	<2015. Studied patients with advanced soft tissue sarcoma who entered EORTC first-line chemotherapy clinical trials between 1980 and 2012: ''The clincial trials in this EORTC-STBSG database contains historical data from patients recruited in clinical trials from the 1980s. Therefore results may be influenced by differences in concomitant standards of care.''

Zoekverantwoording

Database(s): Ovid/Medline, Embase	Datum: 6-6-2023

Periode: 2015-	Talen: nvt

Zoekopbrengst

from 2015 until 06 June 2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs			221
RCTs			274
Observationele studies			
Overig			
Totaal			495

Zoekstrategie

Embase

No.	Query	Results
#39	#37 NOT #38 sleutelartikelen niet gevonden	6
#38	#11 AND #37	17
#37	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 sleutelartikelen	23
#36	'results of randomised studies of the eortc soft tissue and bone sarcoma group (stbsg) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients'	1
#35	'randomized phase iii trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma'	1
#34	'randomized phase ii study of trabectedin and doxorubicin compared with doxorubicin alone as first-line treatment in patients with advanced soft tissue sarcomas: a spanish group for research on sarcoma study'	1
#33	'randomized phase ii evaluation of 6 g/m2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (g-csf) compared with 12 g/m2 of ifosfamide plus doxorubicin and g-csf in the treatment of poor-prognosis soft tissue sarcoma'	1

#32	'randomised phase ii trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma'	1
#31	'picasso 3: a phase 3 international, randomized, double-blind, placebo-controlled study of doxorubicin'	1
#30	'phase iii trial of standard versus dose-intensified doxorubicin, ifosfamide and dacarbazine'	1
#29	'gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (geddis): a randomised controlled phase 3 trial'	1
#28	'brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: an european organisation for research and treatment of cancer soft tissue and bone sarcoma group randomised phase ii and pharmacogenetic study'	1
#27	'efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase ii study of the spanish group for research on sarcomas'	1
#26	'results of randomised studies of the eortc soft tissue and bone sarcoma group (stbsg) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients'	1
#25	'subgroup analysis of older patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide'	1
#24	'doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma'	2
#23	'doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial'	1
#22	'doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma'	1
#21	'phase iii trial of standard versus dose-intensified doxorubicin, ifosfamide and dacarbazine'	1
#20	'first-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone'	1

#19	'aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma'	1
#18	'first-line aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: a phase 2b randomized clinical trial'	1
#17	'a phase iib multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma'	1
#16	'randomized comparison of pazopanib and doxorubicin as first-line treatment in patients with metastatic soft tissue sarcoma'	1
#15	'safety and efficacy of pazopanib in advanced soft tissue sarcoma'	1
#14	'health-related quality-of-life results from palette: a randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior'	1
#13	'pazopanib for metastatic soft-tissue sarcoma' AND graaf AND blay AND palette:ti	1
#12	'clinical practice guidelines for diagnosis, treatment and follow-up' AND gronchi AND 2021 AND 'soft tissue':ti	1
#11	#9 OR #10	619
#10	#6 AND #8 NOT #9 RCT	326
#9	#6 AND #7 SR	293
#8	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	2059851
#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data	733409

	extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#6	#5 AND [2010-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	5107
#5	#3 AND #4	11942
#4	'advanced cancer'/exp OR 'metastasis'/exp OR ((advanced NEAR/4 (cancer OR neoplasm* OR sarcom*)):ti,ab,kw) OR metasta*:ti,ab,kw OR 'locally advanced':ti,ab,kw OR 'primary irresect*':ti,ab,kw	1275529
#3	#1 AND #2	31152
#2	'antineoplastic agent'/exp/mj OR 'cancer immunotherapy'/exp/mj OR 'molecularly targeted therapy'/exp/mj OR (((system* OR chemo OR 'molecular target*') NEAR/3 (treatment OR therap*)):ti,ab,kw) OR chemotherap*:ti,ab,kw OR ifosfamide:ti,ab,kw OR decarbazine:ti,ab,kw OR epirubicin:ti,ab,kw OR temozolomide:ti,ab,kw OR docetaxel:ti,ab,kw OR vinorelbine:ti,ab,kw OR doxorubicin:ti,ab,kw OR paclitaxel:ti,ab,kw OR dactinomycin:ti,ab,kw OR etoposide:ti,ab,kw OR vincristine:ti,ab,kw OR cisplatin:ti,ab,kw OR trabectedin:ti,ab,kw OR imatinib:ti,ab,kw OR sunitinib:ti,ab,kw OR sorafenib:ti,ab,kw OR sirolimus:ti,ab,kw OR everolimus:ti,ab,kw	2080148
#1	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3	106311

	sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 sarcoma*):ti,ab,kw)	

Ovid/Medline

#	Searches	Results
10	(6 and 8) not 9 RCT	241
9	6 and 7 SR	140
8	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1617677
7	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	672162
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	3110
5	limit 4 to yr="2010 -Current"	3200
4	1 and 2 and 3	5725
3	exp Neoplasm Metastasis/ or (advanced adj4 (cancer or neoplasm* or sarcom*)).ti,ab,kf. or metasta*.ti,ab,kf. or locally advanced.ti,ab,kf. or primary irresect*.ti,ab,kf.	767116

2	exp Antineoplastic Agents/ or exp Immunotherapy/ or exp Molecular Targeted Therapy/ or ((system* or chemo or molecular target*) adj3 (treatment or therap*)).ti,ab,kf. or chemotherap*.ti,ab,kf. or ifosfamide.ti,ab,kf. or decarbazine.ti,ab,kf. or epirubicin.ti,ab,kf. or temozolomide.ti,ab,kf. or docetaxel.ti,ab,kf. or vinorelbine.ti,ab,kf. or doxorubicin.ti,ab,kf. or paclitaxel.ti,ab,kf. or dactinomycin.ti,ab,kf. or etoposide.ti,ab,kf. or vincristine.ti,ab,kf. or cisplatin.ti,ab,kf. or trabectedin.ti,ab,kf. or imatinib.ti,ab,kf. or sunitinib.ti,ab,kf. or sorafenib.ti,ab,kf. or sirolimus.ti,ab,kf. or everolimus.ti,ab,kf.	1950723
1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf.	63607

Module 5 – Follow-up: frequentie en duur, beeldvorming

Search and select
A systematic review of the literature was performed to answer the following question:
What is the optimal follow-up strategy in patients with soft tissue sarcomas?
This question can be separated into two subquestions:

1. What is the optimal follow-up duration and frequency in patients with soft tissue sarcomas?
2. What is the optimal follow-up imaging modality in patients with soft tissue sarcomas?

These questions led to the formulation of two PICOs:
PICO 1

P: Patients with soft tissue sarcomas
I: Follow-up duration A
Follow-up frequency A
C: Follow-up duration B
Follow-up frequency B
O: Mortality, quality of life, risk of metastases, risk of recurrence, adverse effects

PICO 2

P: Patients with soft tissue sarcomas
I: MRI as imaging modality during follow-up
C: X-ray and/or CT as imaging modality during follow-up
O: Mortality, quality of life, risk of metastases, risk of recurrence, adverse effects

Relevant outcome measures
The guideline development group considered mortality as a critical outcome measure for decision making; and quality of life, risk of metastases, risk of recurrence, and adverse effects as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the minimal clinical important differences for the outcomes overall survival, progression free survival, and adverse events/toxicity based on the PASKWIL criteria (NVMO, 2018), and for the other outcomes based on relevant literature:

- Overall survival: >12 weeks or hazard ratio <0.7.
- Progression free survival: >12 weeks or hazard ratio <0.7.
- Adverse events and toxicity: lethal <5%, acute or severe <25%.
- Quality of life: The minimum important difference (MID) has been estimated to be a difference of 0.08 or more points for the EQ-5D utility index and seven or more points for the EQ-5D VAS (Pickard, 2007). For quality of life measured with the EORTC QLQ-C30, a difference of 10 points was considered as a clinical important difference (Fiteni 2016).

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until September 19, 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 256 hits. Studies were selected based

on the following criteria: relevant to PICO, cohort study, randomized controlled trial, or systematic review. 7 studies were initially selected based on title and abstract screening. After reading the full text, 5 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 2 studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Puri (2014, and 2018) performed a randomized controlled trial to assess the effect of a follow-up frequency of 3-monthly visits compared to a frequency of 6-monthly visits in 500 patients aged 65 or younger who had a surgical intervention to treat extremity sarcoma, either bone or soft tissue sarcoma (STS). In addition, they compared follow-up using CT-thorax with follow-up using X-thorax. Patients were randomized into four groups with stratification for tumor origin, primary or recurrent presentation, tumor size under or over 8 cm (bone) or 10 cm (soft tissue), tumor grade, and adjuvant chemotherapy. 376 men and 124 women were included, with a median age of 20 years (range 3-65). 359 patients had a bone tumor, and 141 had an STS.

As outcome measures, overall and disease-free survival within 3 years, and detection of pulmonary metastasis were reported. In Puri (2018), overall and disease-free survival within 5 years, and detection of pulmonary metastasis were reported.

For this literature summary, the two reports of the same trial will be referred to as one trial with results on two different follow-up durations.

Results

Mortality

The trial of **Puri (2014 and 2018)** reported on mortality during 3 and 5 years of follow-up. For follow-up with a frequency of one visit per three months, the risk of mortality was 31%, and for six-monthly visits 36% over three years. This resulted in a hazard ratio (HR) of 1.2 (90% confidence interval, CI: not reported to 1.47), indicating a higher risk of mortality with six-month visits compared to visits each three months.

For follow-up with a frequency of one visit per three months, the risk of mortality was 46%, and for six-monthly visits 45% over five years. This resulted in a hazard ratio (HR) of 1.00 (90% confidence interval, CI: not reported to 1.2), indicating a similar risk of mortality with six-month visits compared to three-month visits.

Risk of recurrence

The trial of **Puri (2014 and 2018)** reported on risk of recurrence during 3 and 5 years of follow-up. For follow-up with a frequency of one visit per three months, the risk of recurrence was 48%, and for six-monthly visits 49% over three years. This resulted in a hazard ratio (HR) of 1.01 (90% confidence interval, CI: not reported to 1.2), indicating a slightly higher risk of recurrence with six-month visits compared to visits each three months

For follow-up with a frequency of one visit per three months, the risk of recurrence was 46%, and for six-monthly visits 41% over five years. This resulted in a hazard ratio (HR) of 1.00 (90% confidence interval, CI: not reported to 1.2), indicating a similar risk of recurrence with six-month visits compared to three-month visits.

Level of evidence of the literature

Mortality
The level of evidence regarding the outcome measure *mortality* as related to follow-up frequency started as High (RCT), and was downgraded by two levels because of study limitations (risk of bias due to lack of blinding and differential loss to follow-up); and applicability (bias due to indirectness due to a mixed study population with patients with bone tumors).

Disease-free survival
The level of evidence regarding the outcome measure *mortality* started as High (RCT), and was downgraded by two levels because of study limitations (risk of bias due to lack of blinding and differential loss to follow-up); and applicability (bias due to indirectness due to a mixed study population with patients with bone tumors).

Conclusions
Mortality
Three-year follow-up

Low GRADE	The evidence suggests that six-monthly follow-up visits do not increase or reduce the risk of mortality during three years of follow-up in patients who were being followed-up after having undergone surgery for a soft tissue sarcoma. *Source: Puri, 2014*

Five-year follow-up

Low GRADE	The evidence suggests that six-monthly follow-up visits do not increase or reduce the risk of mortality during five years of follow-up in patients who were being followed-up after having undergone surgery for a soft tissue sarcoma. *Source: Puri, 2018*

Risk of recurrence
Three-year follow-up

Low GRADE	The evidence suggests that six-monthly follow-up visits do not increase or reduce the risk of recurrence during three years of follow-up in patients who were being followed-up after having undergone surgery for a soft tissue sarcoma. *Source: Puri, 2014*

Five-year follow-up

Low GRADE	The evidence suggests that six-monthly follow-up visits do not increase or reduce the risk of recurrence during five years of follow-up in patients who were being followed-up after having undergone surgery for a soft tissue sarcoma. *Source: Puri, 2018*

Kennislacunes
What is the optimal follow-up strategy in patients with soft tissue sarcomas?

1. What is the optimal follow-up duration and frequency in patients with soft tissue sarcomas?
2. What is the optimal follow-up imaging modality in patients with soft tissue sarcomas?

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	geen	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table

Research question: What is the optimal follow-up strategy (duration and frequency) in patients with soft tissue sarcomas?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Puri, 2014	Type of study: Randomized controlled trial Setting and country: Oncology department, Mumbai, India Funding and conflicts of interest: Terry Fox Foundation	Inclusion criteria: 1. Patients operated for primary or recurrent extremity bone & soft tissue sarcomas (both limb salvage and amputations) 2. Non-metastatic at presentation. 3. Reliable for follow-up. Exclusion criteria: Sarcoma not in extremity N total at baseline: Intervention 1: 126 Intervention 2: 123 Intervention 3 126 Intervention 4: 125 Important prognostic factors[2]:	All patients were followed up according to one of these strategies: 1: 3-monthly follow-up visits with CT-thorax 2: 6-monthly follow-up visits with CT-thorax 3: 3-monthly follow-up visits with X-thorax 4: 6-monthly follow-up visits with X-thorax Patients who experienced clinical symptoms that may indicate relapse were counselled for follow-up regardless of schedule.	There was no control procedure, as four strategies were compared	Length of follow-up: 3 years Loss-to-follow-up intention-to-treat; N (%): Intervention 1: 14 (11%) Intervention 2: 8 (6%) Intervention 3: 8 (6%) Intervention 4: 8 (7%) Reasons not reported Loss-to-follow-up intention-to-treat; N (%): Intervention 1: 5 (6%) Intervention 2: 1 (1%) Intervention 3: 4 (3%) Intervention 4: 8 (6%) Reasons not reported Incomplete outcome data: Not reported	Overall survival: 3M: 69% 6M: 64% CT: 66% X-ray: 67% Hazard ratios: 3M vs 6M: 1.2 (90% CI: not reported to 1.47) CT vs X-ray: 0.9 (90% CI: not reported to 1.13 Disease-free survival: 3M: 52% 6M: 51% CT: 49% X-ray: 54% Hazard ratios: 3M vs 6M: 1.01 (90% CI: not reported to 1.2) CT vs X-ray: 0.82 (90% CI: not reported to 0.97	The study indicated that they observed no non-inferiority of either 6-month follow-up strategies. Only trial to assess this subject. No differentiation between bone tumors and soft tissue sarcomas, which would be relevant to this PICO. 90% confidence intervals were reported, which implies a greater probability of false negative results but fits the noninferiority design. Of note, a large majority of patients were diagnosed with recurrence after they reported symptoms that indicated recurrence.

		age median (range): *1: 20 (3-64)* *2: 21 (5-65)* *3: 18 (3-61)* *4: 21 (5-63)* *Sex:* *1: 79 %M* *2: 78 %M* *3: 77 %M* *4: 67 %M* *Soft-tissue sarcoma n (%)* *1: 36 (29%)* *2: 36 (29%)* *3: 33 (26%)* *4: 36 (29%)* Groups comparable at baseline? Yes					
Puri, 2018	Type of study: Randomized controlled trial Setting and country: Oncology department, Mumbai, India Funding and conflicts of interest: Terry Fox Foundation	<u>Inclusion criteria</u>: 1. Patients operated for primary or recurrent extremity bone & soft tissue sarcomas (both limb salvage and amputations) 2. Non-metastatic at presentation. 3. Reliable for follow-up. <u>Exclusion criteria</u>: Sarcoma not in extremity	All patients were followed up according to one of these strategies: 1: 3-monthly follow-up visits with CT-thorax 2: 6-monthly follow-up visits with CT-thorax 3: 3-monthly follow-up visits with X-thorax 4: 6-monthly follow-up visits with X-thorax Patients who experienced clinical symptoms that may indicate relapse were counselled for follow-up regardless of schedule.	There was no control procedure, as four strategies were compared	<u>Length of follow-up</u>: 5 years <u>Loss-to-follow-up intention-to-treat; N (%)</u>: Intervention 1: 5 (11%) Intervention 2: 8 (6%) Intervention 3: 1 (6%) Intervention 4: 5 (7%) Reasons not reported <u>Loss-to-follow-up intention-to-treat; N (%)</u>: Not reported, only compliance to protocol. <u>Incomplete outcome data</u>: Not reported	Overall survival: 3M: 55% 6M: 54% CT: 53% X-ray: 56% Hazard ratios: 3M vs 6M: 1.01 (90% CI: not reported to 1.2) CT vs X-ray: 0.94 (90% CI: not reported to 1.2 Disease-free survival: 3M: 47% 6M: 46% CT: 54% X-ray: 59% Hazard ratios:	The study indicated that they observed no non-inferiority of either 6-month follow-up strategies. Only trial to assess this subject. No differentiation between bone tumors and soft tissue sarcomas, which would be relevant to this PICO. 90% confidence intervals were reported, which implies a greater probability of false negative results but fits the noninferiority design.

		N total at baseline: Intervention 1: 126 Intervention 2: 123 Intervention 3 126 Intervention 4: 125 Important prognostic factors[2]: *age median (range):* *1: 20 (3-64)* *2: 21 (5-65)* *3: 18 (3-61)* *4: 21 (5-63)* *Sex:* *1: 79 %M* *2: 78 %M* *3: 77 %M* *4: 67 %M* *Soft-tissue sarcoma n (%)* *1: 36 (29%)* *2: 36 (29%)* *3: 33 (26%)* *4: 36 (29%)* Groups comparable at baseline? Yes				3M vs 6M: 1.00 (90% CI: not reported to 1.2) CT vs X-ray: 0.74 (90% CI: not reported to 0.9	Of note, a large majority of patients were diagnosed with recurrence after they reported symptoms that indicated recurrence.

Risk of bias table

What is the optimal follow-up strategy (duration and frequency) in patients with soft tissue sarcomas?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Puri, 2014	Definitely yes; Reason: Central randomization stratified for important prognostic factors using computer-generated random permuted blocks.	Definitely yes; Reason: Central telephonic randomization by staff at the Clinical Research Secretariat (trial unit) of the institution.	Definitely no; Reason: Patients, health care providers and outcome assessors were not blinded. No info on data collectors and analysts	Probably no; Reason: Loss to follow-up was frequent in different study arms, and also differential over the study arms. No reasons were reported. No imputation methods were used.	Definitely yes; Reason: All relevant outcomes were prespecified in a trial register (NCT 00384735, clinicaltrials.gov). and reported	Definitely yes; Reason: No other problems noted	**Some concerns**

Puri, 2018	Definitely yes; Reason: Central randomization stratified for important prognostic factors using computer-generated random permuted blocks.	Definitely yes; Reason: Central telephonic randomization by staff at the Clinical Research Secretariat (trial unit) of the institution.	Definitely no; Reason: Patients, health care providers and outcome assessors were not blinded. No info on data collectors and analysts	Probably no; Reason: Loss to follow-up was frequent in different study arms, and also differential over the study arms. No reasons were reported. No imputation methods were used.	Definitely yes; Reason: All relevant outcomes were prespecified in a trial register (NCT 00384735, clinicaltrials.gov). and reported	Definitely yes; Reason: No other problems noted	**Some concerns**

Table of excluded studies

Reference	Reason for exclusion
Park, J. W., Yoo, H. J., Kim, H. S., Choi, J. Y., Cho, H. S., Hong, S. H., & Han, I. (2019). MRI surveillance for local recurrence in extremity soft tissue sarcoma. Eur J Surg Oncol, 45(2), 268-274. https://doi.org/10.1016/j.ejso.2018.08.032	Wrong comparison
Park SY, Chung HW, Chae SY, Lee JS. Comparison of MRI and PET-CT in detecting the loco-regional recurrence of soft tissue sarcomas during surveillance. Skeletal Radiol. 2016 Oct;45(10):1375-84. doi: 10.1007/s00256-016-2440-5. Epub 2016 Aug 3. PMID: 27488833.	Wrong comparison
Gorelik N, Reddy SMV, Turcotte RE, Goulding K, Jung S, Alcindor T, Powell TI. Early detection of metastases using whole-body MRI for initial staging and routine follow-up of myxoid liposarcoma. Skeletal Radiol. 2018 Mar;47(3):369-379. doi: 10.1007/s00256-017-2845-9. Epub 2017 Dec 23. PMID: 29275455.	No comparison
Morgan JE, Harden M, Phillips RS. Does routine surveillance imaging after completing treatment for childhood solid tumours cause more harm than good? A systematic review and meta-analysis protocol. Syst Rev. 2019 Jul 12;8(1):168. doi: 10.1186/s13643-019-1096-3. PMID: 31300033; PMCID: PMC6624999.	Protocol
Giglio V, Schneider P, Madden K, Lin B, Multani I, Baldawi H, Thornley P, Naji L, Levin M, Wang P, Bozzo A, Wilson D, Ghert M. Published randomized controlled trials of surveillance in cancer patients - a systematic review. Oncol Rev. 2021 Jun 24;15(1):522. doi: 10.4081/oncol.2021.522. PMID: 34267889; PMCID: PMC8256375.	Wrong population
Dammerer D, VAN Beeck A, Schneeweiss V, Schwabegger A. Follow-up Strategies for Primary Extremity Soft-tissue Sarcoma in Adults: A Systematic Review of the Published Literature. In Vivo. 2020 Nov-Dec;34(6):3057-3068. doi: 10.21873/invivo.12140. PMID: 33144410; PMCID: PMC7811670.	Narrative review
SAFETY Investigators. The Surveillance After Extremity Tumor Surgery (SAFETY) trial: protocol for a pilot study to determine the feasibility of a multi-centre randomised controlled trial. BMJ Open. 2019 Sep 18;9(9):e029054. doi: 10.1136/bmjopen-2019-029054. PMID: 31537562; PMCID: PMC6756324.	Protocol

Zoekverantwoording
Algemene informatie

Richtlijn: NVVH- Wekedelentumoren	
Uitgangsvraag: What is the optimal follow-up strategy (duration and frequency) in patients with soft tissue sarcomas?	
Database(s): Ovid/Medline, Embase	Datum: 14-9-2022, 19-9-2022
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	

Toelichting:

19-9-2022

De werkgroep geeft aan minder specifiek te willen zoeken en komt met de volgende terminologie:

Mpnst, Synoviosarcoom, Myxofibrosarcoom, Ups, Nos, Leyomyosarcoom, Spoelcel sarcoom, Myxoid liposarcoom

De zoekstrategie wordt aangepast, opnieuw ontdubbeld en in Rayyan geplaatst. Het vorige resultaat is verwijderd.

14-9-2022

Voor deze vraag is gezocht met de volgende concepten:

Soft tissue cancer/sarcoma AND Follow up or surveillance AND (CT OR MRI OR mortality OR survival OR recurrence OR quality of life)

Alhoewel deze vraag is opgezet als een interventievraag is ook met de outcome gezocht omdat de combinatie follow up en soft tissue cancer in 1 database meer dan 70.000 referenties opleverde. Omdat de relevante sleutelartikelen niet allemaal gevonden werden met de outcome is ook de combinatie met CT of MRI toegevoegd.

Omdat chondrosarcoma en osteosarcoma onderdeel uitmaken van de Emtree Sarcoma en deze in Embase niet gemakkelijk afzonderlijk te zoeken zijn, is handmatig een selectie gemaakt in Embase van deze studies, die vervolgens zijn geëxcludeerd. #16, #17

Van de 6 sleutelartikelen werden er twee niet gevonden omdat het richtlijnen/rapporten betrof. Van de overige 4 artikelen werd het artikel van Eilber niet gevonden omdat in title, keyword en indexterm niet werd gesproken over follow up. Uiteindelijk wordt vanwege de tijdslimiet alleen het artikel van Rothermund gevonden

F. Eilber et al, High-grade extremity soft tissue sarcomas: factors predictive of local recurrence and its effect on morbidity and mortality, Annals of Surgery, 2003, 237(2):218-26

C. Rothermundt et al, What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients, British journal of Cancer, 2014, 110, 2420–2426

Te gebruiken voor richtlijnen tekst:
In de databases Embase en Ovid/Medline is op 19-9-2022 met relevante zoektermen gezocht naar SRs, RCTs en observationele studies over de follow up bij wekedelentumoren. De literatuurzoekactie leverde 256 unieke treffers op.

Zoekopbrengst

19-9-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	20	11	22
RCTs	8	12	13
Observationele studies	212	67	221
Overig			
Totaal			256
14-9-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	44	20	52
RCTs	34	28	41
Observationele studies	648	205	696
Overig			
Totaal			789

Zoekstrategie

Embase

19-9-2022

No.	Query	Results
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#26	#8 AND #24	**3**
#25	#19 AND #24	**1**
#24	#20 OR #21 OR #22 OR #23	**4**
#23	extremity AND soft AND tissue AND sarcoma AND patient AND 'follow up' AND tumor AND grade AND size AND affect AND surveillance AND strategies AND after AND potentially AND curative AND surgery	**1**

No.	Query	Results
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#21	'high grade' AND extremity AND soft AND tissue AND sarcomas AND factors AND p redictive AND of AND local AND recurrence AND its AND effect AND on AND morbidity AND mortality	**1**
#20	what AND is AND the AND role AND routine AND 'follow up' AND for AND localised AND limb AND soft AND tissue AND a AND retrosp ective AND analysis AND of AND 174 AND patients	**1**
#19	#14 OR #15 OR #16	**240**
#18	#16 NOT #15 NOT #14	**212**
#17	#15 NOT #14	**8**
#16	#9 AND (#12 OR #13)	**226**
#15	#9 AND #11	**12**
#14	#9 AND #10	**20**
#13	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical	**13457242**

No.	Query	Results
	study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#12	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**7257577**
#11	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	**1959385**
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	**859072**

No.	Query	Results
#9	#8 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**349**
#8	#2 AND #3 AND #7	**612**
#7	#4 OR #5 OR #6	**7191535**
#6	'mortality'/exp OR 'survival'/exp OR 'recurrent disease'/exp OR 'cancer recurrence'/exp OR 'quality of life'/exp OR surviv*:ti,ab,kw OR mortalit*:ti,ab,kw OR recurre*:ti,ab,kw OR relaps*:ti,ab,kw	**4999701**
#5	'nuclear magnetic resonance imaging'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti	**1441067**
#4	'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	**1589128**
#3	'follow up'/exp/mj OR 'follow up':ti,kw OR followup:ti,kw OR surveill*:ti,kw	**258825**
#2	'soft tissue sarcoma'/exp OR 'malignant peripheral nerve sheath tumor'/exp OR 'synovial sarcoma'/exp OR 'fibromyxosarcoma'/exp OR 'undifferentiated pleomorphic sarcoma'/exp OR 'leiomyosarcoma'/exp OR 'myxosarcoma'/exp OR 'spindle cell sarcoma'/exp OR 'neurofibrosarcoma'/exp OR 'neurofibrosarcoma*':ti,ab,kw OR 'neurogenic sarcoma*':ti,ab,kw OR 'fusiform cell sarcoma*':ti,ab,kw OR 'fusocellular sarcoma*':ti,ab,kw OR 'spindle cell sarcoma*':ti,ab,kw OR 'myxoid liposarcoma*':ti,ab,kw OR 'myxosarcoma*':ti,ab,kw OR 'leio myosarcoma*':ti,ab,kw OR 'leiomyoplastic sarcoma*':ti,ab,kw OR 'leiomyosarcoma*':ti,ab,kw OR 'undifferentiated pleomorphic sarcoma*':ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR 'malignant synovioma':ti,ab,kw OR (((synovi* OR nos) NEAR/3 sarcoma*):ti,ab,kw) OR 'synoviasarcoma*':ti,ab,kw OR 'synoviosarcoma*':ti,ab,kw OR 'tendosynovial sarcoma*':ti,ab,kw OR 'malignant peripheral nerve sheath tumor':ti,ab,kw OR 'malignant peripheral nerve sheath tumour':ti,ab,kw OR (('soft tissue' NEAR/4 (sarcoma* OR tumor* OR tumour* OR neoplasm* OR cancer*)):ti,ab,kw)	**96757**

14-9-2022

No.	Query	Results
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#38	#33 OR #36 OR #37	726
#37	#35 NOT #34 NOT #33 OBS	648
#36	#34 NOT #33 RCT	34
#35	#28 AND (#31 OR #32)	981
#34	#28 AND #30	42
#33	#28 AND #29 SR	44
#32	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13447530
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No.	Query	Results
	(study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
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#28	#17 OR #27	1351
#27	#26 NOT #16	740
#26	#24 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	548
#25	#5 AND #24 sleutelartikelen	3
#24	#19 AND #20 AND #23	1013
#23	#21 OR #22	2647285
#22	'nuclear magnetic resonance imaging'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti	1439909
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#19	'sarcoma'/exp/mj OR 'desmoplastic small round cell tumor'/exp OR 'endometrial stromal tumor'/exp OR 'soft tissue tumor'/exp OR 'phyllodes	449018

No.	Query	Results
	tumor'/exp OR (((desmoplastic OR stromal OR rhabdoid* OR phyllo* OR 'soft tissue') NEAR/4 (tumor* OR tumour* OR neoplasm* OR cancer*)):ti,ab,kw) OR 'histioblastoma*':ti,ab,kw OR 'histiosarcoma*':ti,ab,kw OR 'sarcoma*':ti,ab,kw OR 'fibroadenosarcoma*':ti,ab,kw OR 'fibrosarcoma*':ti,ab,kw OR 'angioendotheliosarcoma*':ti,ab,kw OR 'angiosarcoma*':ti,ab,kw OR 'haemangiosarcoma*':ti,ab,kw OR 'hemangio endotheliosarcoma*':ti,ab,kw OR 'hemangioendotheliosarcoma*':ti,ab,kw OR 'hemangiosarcoma*':ti,ab,kw OR 'malignant angioendothelioma*':ti,ab,kw OR 'malignant epithelioid hemangioendothelioma*':ti,ab,kw OR 'malignant haemangioendothelioma*':ti,ab,kw OR 'malignant hemangioendothelioma*':ti,ab,kw OR 'fibroxanthosarcoma':ti,ab,kw OR ((malignant NEAR/3 (histiocytoma* OR fibroxanthoma*)):ti,ab,kw) OR 'leiomyosarcoma*':ti,ab,kw OR liposarcoma*:ti,ab,kw OR myxosarcoma*:ti,ab,kw OR 'lymphangiosarcoma*':ti,ab,kw OR 'malignant lymphangioendothelioma*':ti,ab,kw OR neurofibrosarcoma*:ti,ab,kw OR adenosarcoma*:ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR gliosarcoma*:ti,ab,kw OR myosarcoma*:ti,ab,kw OR rhabdomyosarcoma*:ti,ab,kw OR dermatofibrosarcoma*:ti,ab,kw OR cystosarcoma*:ti,ab,kw OR (gist:ti AND (tumor*:ti OR tumour*:ti)) OR (gist:ab AND (tumor*:ab OR tumour*:ab)) OR (((locali* OR solitar*) NEAR/2 fibrous NEAR/2 (tumor* OR tumour*)):ti,ab,kw)	
#18	#5 AND #12 sleutelartikelen	2
#17	#13 NOT #15	981
#16	l2015258945:id OR l2015585868:id OR l2018129090:id OR l2015522731:id OR l2018779225:id OR l2017015298:id OR l2015685540:id OR l636944321:id OR l2007174898:id OR l2011855092:id OR l2019542000:id OR l2007586559:id OR l635377748:id OR l633410236:id OR l2007326523:id OR l632518658:id OR l632334512:id OR l2004282874:id OR l2005932127:id OR l2007085342:id OR l629556306:id OR l2001636100:id OR l622800275:id OR l627276533:id OR l2002270611:id OR l2004687871:id OR l627781507:id OR l633967199:id OR l624302799:id OR l620126600:id OR l621113414:id OR l624837345:id OR l617838873:id OR l618922893:id OR l617136781:id OR l613562199:id OR l618278456:id OR l621715795:id OR l614483621:id OR l617174259:id OR l610987267:id OR l611202173:id OR l613873021:id OR l614222056:id OR l614926797:id OR l618231733:id OR l616106663:id OR l612301409:id OR l606963975:id OR l611436070:id OR l610220547:id OR l609389455:id OR l605416782:id OR l617441017:id OR l52926343:id OR l604054350:id OR l52534971:id OR l372899698:id OR l52827946:id OR l373552243:id OR l600555048:id OR l604598099:id OR l51788032:id OR l369597579:id OR l52045673:id OR l563066215:id OR l52039637:id OR l365700856:id OR l365814687:id OR l52050245:id OR l365083789:id OR l364008926:id OR l363000989:id OR l361892493:id OR l361579181:id OR l361169684:id OR l360029232:id OR l50893929:id OR l359125166:id OR l358406263:id OR l359938691:id OR l358070723:id OR l354748709:id OR l354682658:id OR l354710975:id OR l354618334:id OR l354049050:id OR l354455758:id OR l352544760:id OR l352544761:id OR l351167206:id OR l47343670:id OR l352544705:id OR l46674904:id OR l47585266:id OR l44846067:id OR l44496361:id OR l44080805:id OR l43676798:id OR l43879543:id	150

No.	Query	Results
	OR l43614677:id OR l41713121:id OR l41279362:id OR l40674617:id OR l41348864:id OR l40283446:id OR l40879600:id OR l40153225:id OR l39411226:id OR l37039033:id OR l36605152:id OR l36044255:id OR l34734474:id OR l43930569:id OR l32755476:id OR l32655099:id OR l33487771:id OR l30650559:id OR l30601522:id OR l28533502:id OR l27467748:id OR l27397900:id OR l127272080:id OR l27057456:id OR l26101838:id OR l126425337:id OR l26023407:id OR l26143058:id OR l25133335:id OR l22367433:id OR l22982426:id OR l22834225:id OR l21188250:id OR l21022524:id OR l21744797:id OR l20317328:id OR l20073387:id OR l18200549:id OR l18173157:id OR l17740343:id OR l16741902:id OR l16688680:id OR l15011017:id OR l14088279:id OR l14079024:id OR l13040820:id OR l13040821:id OR l11052889:id OR l9129425:id OR l10148187:id Chondrosarcoma osteosarcoma	
#15	#13 AND #14	182
#14	'chondrosarcoma'/exp OR 'osteosarcoma'/exp	51962
#13	#12 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	936
#12	#9 AND #10 AND #11	1833
#11	'mortality'/exp OR 'survival'/exp OR 'recurrent disease'/exp OR 'cancer recurrence'/exp OR 'quality of life'/exp OR surviv*:ti,ab,kw OR mortalit*:ti,ab,kw OR recurre*:ti,ab,kw OR relaps*:ti,ab,kw	4995343
#10	'follow up'/exp/mj OR 'follow up':ti,kw OR followup:ti,kw OR surveill*:ti,kw	258659
#9	'sarcoma'/exp/mj OR 'desmoplastic small round cell tumor'/exp OR 'endometrial stromal tumor'/exp OR 'soft tissue tumor'/exp OR 'phyllodes tumor'/exp OR (((desmoplastic OR stromal OR rhabdoid* OR phyllo* OR 'soft tissue') NEAR/4 (tumor* OR tumour* OR neoplasm* OR cancer*)):ti,ab,kw) OR 'histioblastoma*':ti,ab,kw OR 'histiosarcoma*':ti,ab,kw OR 'sarcoma*':ti,ab,kw OR 'fibroadenosarcoma*':ti,ab,kw OR 'fibrosarcoma*':ti,ab,kw OR 'angioendotheliosarcoma*':ti,ab,kw OR 'angiosarcoma*':ti,ab,kw OR 'haemangiosarcoma*':ti,ab,kw OR 'hemangioendotheliosarcoma*':ti,ab,kw OR 'hemangioendotheliosarcoma*':ti,ab,kw OR 'hemangiosarcoma*':ti,ab,kw OR 'malignant angioendothelioma*':ti,ab,kw OR 'malignant epithelioid hemangioendothelioma*':ti,ab,kw OR 'malignant haemangioendothelioma*':ti,ab,kw OR 'malignant hemangioendothelioma*':ti,ab,kw OR 'fibroxanthosarcoma':ti,ab,kw OR ((malignant NEAR/3 (histiocytoma* OR fibroxanthoma*)):ti,ab,kw) OR 'leiomyosarcoma*':ti,ab,kw OR liposarcoma*:ti,ab,kw OR myxosarcoma*:ti,ab,kw OR 'lymphangiosarcoma*':ti,ab,kw OR 'malignant lymphangioendothelioma*':ti,ab,kw OR neurofibrosarcoma*:ti,ab,kw OR adenosarcoma*:ti,ab,kw OR 'fibromyxosarcoma*':ti,ab,kw OR 'myxofibrosarcoma*':ti,ab,kw OR gliosarcoma*:ti,ab,kw OR myosarcoma*:ti,ab,kw OR rhabdomyosarcoma*:ti,ab,kw OR dermatofibrosarcoma*:ti,ab,kw OR cystosarcoma*:ti,ab,kw OR (gist:ti AND	449018

No.	Query	Results
	(tumor*:ti OR tumour*:ti)) OR (gist:ab AND (tumor*:ab OR tumour*:ab)) OR (((locali* OR solitar*) NEAR/2 fibrous NEAR/2 (tumor* OR tumour*)):ti,ab,kw)	
#8	#6 OR #7	2647285
#5	#1 OR #2 OR #3 OR #4 sleutelartikelen	4
#4	extremity AND soft AND tissue AND sarcoma AND patient AND 'follow up' AND tumor AND grade AND size AND affect AND surveillance AND strategies AND after AND potentially AND curative AND surgery	1
#3	detection AND local AND recurrences AND of AND limb AND soft AND tissue AND sarcomas AND is AND magnetic AND resonance AND imaging AND labarre AND 2009 AND european AND journal AND radiology	1
#2	'high grade' AND extremity AND soft AND tissue AND sarcomas AND factors AND predictive AND of AND local AND recurrence AND its AND effect AND on AND morbidity AND mortality	1
#1	what AND is AND the AND role AND routine AND 'follow up' AND for AND localised AND limb AND soft AND tissue AND a AND retrospective AND analysis AND of AND 174 AND patients	1

Ovid/Medline

19-9-2022

#	Searches	Results
16	14 not 13 not 12 OBS	67
15	13 not 12 RCT	12
14	7 and (11 or 12)	87
13	7 and 9	13
12	7 and 8 SR	11
11	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow	5248790

	up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
10	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4248410
9	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1546706
8	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	618451
7	6 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	238
6	limit 5 to yr="2010 -Current"	240
5	1 and 2 and (3 or 4)	354
4	exp Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf. or exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	1566159
3	exp Mortality/ or exp Survival/ or exp Recurrence/ or exp Neoplasm Recurrence, Local/ or exp "Quality of Life"/ or surviv*.ti,ab,kf. or mortalit*.ti,ab,kf. or recurre*.ti,ab,kf. or relaps*.ti,ab,kf.	3132853
2	*Follow-Up Studies/ or follow up.ti,kf. or followup.ti,kf. or surveill*.ti,kf.	182376

1	Neurofibrosarcoma/ or *Sarcoma/ or Leiomyosarcoma/ or Myxosarcoma/ or Sarcoma, Synovial/ or myxoid liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or leio myosarcoma*.ti,ab,kf. or leiomyoplastic sarcoma*.ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or undifferentiated pleomorphic sarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or malignant synovioma.ti,ab,kf. or ((synovi* or nos) adj3 sarcoma*).ti,ab,kf. or synoviasarcoma*.ti,ab,kf. or synoviosarcoma*.ti,ab,kf. or tendosynovial sarcoma*.ti,ab,kf. or malignant peripheral nerve sheath tumor.ti,ab,kf. or malignant peripheral nerve sheath tumour.ti,ab,kf. or (soft tissue adj4 (sarcoma* or tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf. Zoekblok aangepast	61632

14-9-2022

#	Searches	Results
16	14 not 13 not 12 OBS	205
15	13 not 12 RCT	28
14	7 and (11 or 12)	247
13	7 and 9	30
12	7 and 8 SR	20
11	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5246523
10	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-	4246061

	sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	
9	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1545869
8	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	617909
7	6 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	605
6	limit 5 to yr="2010 -Current"	617
5	1 and 2 and (3 or 4)	960
4	exp Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf. or exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	1565386
3	exp Mortality/ or exp Survival/ or exp Recurrence/ or exp Neoplasm Recurrence, Local/ or exp "Quality of Life"/ or surviv*.ti,ab,kf. or mortalit*.ti,ab,kf. or recurre*.ti,ab,kf. or relaps*.ti,ab,kf.	3131303
2	*Follow-Up Studies/ or follow up.ti,kf. or followup.ti,kf. or surveill*.ti,kf.	182299
1	exp Soft Tissue Neoplasms/ or Sarcoma/ or Adenosarcoma/ or Carcinosarcoma/ or Desmoplastic Small Round Cell Tumor/ or Endometrial Stromal Tumors/ or Fibrosarcoma/ or Hemangiosarcoma/ or Histiocytoma, Malignant Fibrous/ or Leiomyosarcoma/ or Liposarcoma/ or Lymphangiosarcoma/ or Mixed Tumor, Mesodermal/ or Myosarcoma/ or Myxosarcoma/ or Osteosarcoma/ or Phyllodes Tumor/ or Sarcoma, Alveolar Soft Part/ or Sarcoma, Clear Cell/ or Sarcoma, Experimental/ or Sarcoma, Kaposi/ or Sarcoma, Myeloid/ or Sarcoma, Small Cell/ or Sarcoma, Synovial/ or ((desmoplastic or stromal or rhabdoid* or phyllo* or soft tissue) adj4 (tumor* or tumour* or neoplasm* or cancer*)).ti,ab,kf. or	239953

	histioblastoma*.ti,ab,kf. or histiosarcoma*.ti,ab,kf. or sarcoma*.ti,ab,kf. or fibroadenosarcoma*.ti,ab,kf. or fibrosarcoma*.ti,ab,kf. or angioendotheliosarcoma*.ti,ab,kf. or angiosarcoma*.ti,ab,kf. or haemangiosarcoma*.ti,ab,kf. or hemangio endotheliosarcoma*.ti,ab,kf. or hemangioendotheliosarcoma*.ti,ab,kf. or hemangiosarcoma*.ti,ab,kf. or malignant angioendothelioma*.ti,ab,kf. or malignant epithelioid hemangioendothelioma*.ti,ab,kf. or malignant haemangioendothelioma*.ti,ab,kf. or malignant hemangioendothelioma*.ti,ab,kf. or fibroxanthosarcoma.ti,ab,kf. or (malignant adj3 (histiocytoma* or fibroxanthoma*)).ti,ab,kf. or leiomyosarcoma*.ti,ab,kf. or liposarcoma*.ti,ab,kf. or myxosarcoma*.ti,ab,kf. or lymphangiosarcoma*.ti,ab,kf. or malignant lymphangioendothelioma*.ti,ab,kf. or neurofibrosarcoma*.ti,ab,kf. or adenosarcoma*.ti,ab,kf. or fibromyxosarcoma*.ti,ab,kf. or myxofibrosarcoma*.ti,ab,kf. or gliosarcoma*.ti,ab,kf. or myosarcoma*.ti,ab,kf. or rhabdomyosarcoma*.ti,ab,kf. or dermatofibrosarcoma*.ti,ab,kf. or cystosarcoma*.ti,ab,kf. or (gist and (tumor* or tumour*)).ti. or (gist and (tumor* or tumour*)).ab. or ((locali* or solitar*) adj2 fibrous adj2 (tumor* or tumour*)).ti,ab,kf.	

Module 6 – Doorverwijzen specialistisch centrum/MDO

Samenvatting literatuur

De aanbevelingen zijn, gezien de aard van de uitgangsvraag en de specifieke Nederlandse situatie, uitsluitend gebaseerd op overwegingen. Deze overwegingen zijn opgesteld door de werkgroepleden op basis van kennis uit de praktijk en waar mogelijk onderbouwd door niet systematisch literatuuronderzoek

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	Minimaal, tgv verdere centralisatie	-	-	netwerkvorming	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Module 7 – Subtypen met bijzondere zorgpaden

Samenvatting literatuur

De aanbevelingen zijn, gezien de aard van de uitgangsvraag en de specifieke Nederlandse situatie, uitsluitend gebaseerd op overwegingen. Deze overwegingen zijn opgesteld door de werkgroepleden op basis van kennis uit de praktijk en waar mogelijk onderbouwd door niet systematisch literatuuronderzoek.

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	Minimaal, tgv verdere centralisatie	-	-	netwerkvorming	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Module 8 – Pathologie

Samenvatting literatuur

De aanbevelingen zijn uitsluitend gebaseerd op overwegingen. Deze overwegingen zijn opgesteld door de werkgroepleden op basis van kennis uit de praktijk en waar mogelijk onderbouwd door niet-systematisch literatuuronderzoek en de ESMO guideline (Gronchi, 2021).

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	Geen nieuwe behandelvormen voorgesteld	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

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Module 9 – Patiëntenvoorlichting

Samenvatting literatuur

Voor deze module is geen literatuur search verricht. De aanbevelingen zijn gebaseerd op overwegingen van de werkgroep. Deze overwegingen komen voort uit kennis uit de praktijk. Waar nodig worden de overwegingen onderbouwd met niet-systematisch gezochte literatuur en gebruikmakende van internationale richtlijnen.

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
1e	1-3	geen	-	-	geen	nvt	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

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