# Bijlagen
# Cluster Borstkanker
# Conceptrichtlijnmodules
## Derde cyclus - deel a 2026

# Inhoudsopgave

# Bijlagen bij module Beeldvormende diagnostiek bij oligometastasen bij borstkanker

**Background**

Oligometastatic disease in breast cancer is commonly defined as up to five metastatic lesions, though exact definitions vary across the literature (Gerke 2025; Lievens 2020). Patients with a single metastasis exhibit better prognosis than those with multiple lesions, and curative treatment may be considered for one or two metastases (Yoon 2024; Steenbruggen 2021; van Ommen 2023). This disease state can present synchronously at initial diagnosis, metachronously after initial treatment, or as oligoprogression during otherwise stable metastatic disease (Yoon 2024; Lievens 2020).

Precise imaging to determine the number and location of metastases is critical for selecting appropriate oligometastasis-directed therapies. FDG-PET/CT, CT, and MRI are widely used, but their choice and sequencing lack standardization (Gerke 2025; Yoon 2024). Imaging may yield non-specific findings, and when biopsy is not feasible, non-invasive diagnosis relies heavily on imaging accuracy (Gerke 2025).

A head-to-head comparison in metastatic breast cancer demonstrated that FDG-PET/CT detected additional metastases more frequently than conventional CT (Moser 2024). In oligometastatic breast cancer, FDG-PET/CT identified additional metastases in about one-third of patients compared to CT, significantly impacting disease classification and potential treatment approaches (Moser 2024). PET/MRI has also shown greater sensitivity and specificity than PET/CT in detecting distant metastases in breast cancer (Bruckmann 2021). Clinical practice shows considerable variation, and the incremental value of combining imaging modalities—such as MRI after PET-positive findings in the spine, pelvis, or liver—remains unclear (Gerke 2025; Yoon 2024). This diagnostic uncertainty contributes to both underdiagnosis and overdiagnosis, which may adversely influence treatment decisions and patient outcomes.

Clarifying the diagnostic accuracy and utility of individual and combined imaging strategies may help standardize guideline recommendations. Enhanced diagnostic precision could support more targeted imaging, fewer unnecessary procedures, and more sensitive identification of true oligometastatic disease. Considerations of cost-effectiveness and consistency across clinical settings are essential for future guideline development.

Given the broad scope of this topic, the guideline panel prioritized a focused quantitative analysis and GRADE assessment for question 1, which evaluates the incremental diagnostic value of MRI (spine/pelvis or liver) after a positive FDG-PET/CT in detecting oligometastases in breast cancer. This question directly addresses a common diagnostic dilemma in clinical practice and is central to optimizing imaging strategies in this setting. Question 2 explores the role of emerging PET tracers (such as FES, NaF, PSMA, Fluciclovine, and FAPI) for characterizing suspicious lesions or confirming oligometastases or oligoprogression in (different types of) breast cancer. Given the early and heterogeneous evidence base, this question is addressed qualitatively and serves to contextualize the potential of novel tracers for future clinical practice and guideline development.

**Search and select**

The ideal body of evidence would include studies that directly compare the test strategies under consideration (i.e., randomized trials) and the resulting interventions and consequences (i.e., patient-important outcomes). Such studies would, by design, address all

of the issues in the analytical framework and allow guideline panelists to apply the familiar GRADE approach for interventions' (Schünemann, 2019). For most tests or test and treat strategies, however, this direct evidence does not exist. Therefore, a search question on test accuracy outcomes is formulated, whereby linked evidence that connects test accuracy to downstream consequences is required for decision-making.

A systematic review of the literature was performed to answer the following question(s): What is the incremental diagnostic accuracy of targeted MRI (spine/pelvis or liver) compared to FDG-PET/CT alone for detecting additional (oligo)metastases in breast cancer patients with suspected bone oligometastases?

PICO 1 (impact outcomes)
PICRO 2 (diagnostic test accuracy outcomes)

**Table 1. PIC(R)O's**

| | PICO 1<br>Impact outcomes | PICRO 2<br>Diagnostic test accuracy outcomes |
|---|---|---|
| Patients | Patients with breast cancer with suspected (oligo)metastasis on FDG-PET/CT | Zie PICO1 |
| Index test | Targeted MRI (spine, pelvis, liver) | Measure: High-resolution anatomical and functional imaging.<br>Procedure: Dedicated regional MRI (e.g., spine or liver) using contrast-enhanced T1/T2 sequences and/or diffusion-weighted imaging.<br>Cut-off: Lesion characteristics on MRI signal.<br>Position: Typically an add-on test when PET/CT identifies equivocal or suspicious lesions. |
| Comparator test | [$^{18}$F]FDG PET/CT alone | Measure: Uptake of fluorodeoxyglucose indicating metabolic activity.<br>Procedure: Whole-body imaging post 60 min FDG injection.<br>Cut-off: Visual interpretation or SUVmax thresholds (varies per study).<br>Position: Often used as a replacement for conventional staging (CT + BS), or as a triage tool to determine need for further imaging. |
| Reference test | NA | Pathological examination or a clinical diagnosis based on expert opinion or follow-up. |
| Outcomes | Change in management, additional metastasis | Test accuracy outcomes (sensitivity and specificity, PPV, NPV and area under the curve) |
| Other selection criteria | Study design: systematic reviews, randomized controlled trials and observational studies | Study design: systematic reviews |

<u>Relevant outcome measures</u>
The guideline panel considered sensitivity and NPV as a critical outcome measure for decision making; and specificity and PPV as an important outcome measure for decision making.

**Table 2. Consequences of diagnostic test characteristics**

| Outcome | Consequences | Relevance |
|---|---|---|
| True positives (TP) | Correctly identifying oligometastases is essential for initiating appropriate treatment, such as metastasis-directed therapy. | Critical |
| True negatives (TN) | Supports confidence in ruling out disease and avoids overtreatment, but has less direct impact on patient outcomes compared to TP or FN. | Important |
| False positives (FP) | May result in overtreatment or unnecessary diagnostic follow-up, but the clinical consequences are generally reversible or manageable. | Important |
| False negatives (FN) | A missed metastasis can lead to undertreatment, unjustified reassurance about limited disease, and potentially worse clinical outcomes. | Critical |

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

Per outcome measure the guideline panel defined the following minimal clinically (patient) important difference:

- Sensitivity:
  A minimum threshold of ≥90% was considered clinically important. This reflects the priority of minimizing false negatives to ensure that patients with oligometastatic disease are correctly identified for potential curative treatment.
- Specificity:
  A minimum threshold of ≥80% was considered clinically important. While secondary to sensitivity, this level helps reduce false positives and avoids unnecessary interventions in patients without oligometastases.
- Positive Predictive Value (PPV):
  A minimum threshold of ≥85% was considered clinically important. This ensures that a positive imaging result has a high likelihood of representing true disease, which is critical for initiating intensive or invasive treatment.
- Negative Predictive Value (NPV):
  A minimum threshold of ≥90% was considered clinically important. A high NPV is essential to reliably exclude oligometastases and support treatment decisions such as omission of metastasis-directed therapy.

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2019 to 26-5-2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from the following primary search

concepts: (1) Metastasis OR oligometastases, (2) MRI-PET OR FDG-PET, MRI, FES-PET, FAPI-PET OR 4-fase-CT, (3) Breast cancer. Duplicates were removed using EndNote software. After deduplication and selection of systematic reviews a total of 107 records were imported for title/abstract screening. Studies were selected based on the following criteria:

- Systematic reviews (searched in at least two databases, detailed search strategy with search date, in- and exclusion criteria, exclusion table, risk of bias assessment and results of individual studies available);
- Full-text English language publication; and
- Studies according to the PICROTS.

Because of the large body of literature, the guideline committee decided to initially search for systematic reviews only, with the option to extend the search to individual studies if the results from the systematic reviews would be deemed insufficient.

Initially, 19 systematic reviews were selected based on title and abstract screening. After reading the full text, 18 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study was included (Xia 2023). Although this review provides valuable pooled diagnostic accuracy data for FDG-PET/CT and PET/MRI in breast cancer, the evidence should be considered indirect. The search strategy was broad and included MRI of the spine, pelvis, and liver, but the available studies reported diagnostic accuracy primarily for bone metastases. This means the indirectness applies both to the disease setting (general metastatic rather than oligometastatic) and to the anatomical focus (bone metastases rather than the full scope of the search). The guideline panel therefore included Xia (2023) as the best available systematic review evidence, but downgraded the certainty of evidence for indirectness.

In parallel, all identified studies were reviewed for relevance to subquestion 2. Zhang (2024) compared $^{68}$Ga-FAPI PET/CT with $^{18}$F-FDG PET/CT in breast cancer and provides supporting evidence for question 3 on the value of new PET tracers in detecting or confirming oligometastases or oligoprogression. Although it does not directly address additive imaging strategies or clinical subgroups, it offers contextual insight into tracer performance. This review is not included in the summary of literature or GRADE assessment but is described narratively in the considerations.

**Summary of literature**

Description of studies

One systematic review was included in the analysis of the literature (Xia 2023). Important study characteristics and results are summarized in table 3. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Xia (2023) conducted a systematic review and meta-analysis to compare the diagnostic efficacy of [$^{18}$F]FDG PET/CT and [$^{18}$F]FDG PET/MRI with other imaging modalities—including contrast-enhanced CT (CECT), MRI, bone scintigraphy (BS), and ultrasound (US)—for detecting metastases in patients with breast cancer. A comprehensive literature search was performed across PubMed, Embase, Web of Science, and the Cochrane Library from inception to February 2023.

Studies were included if they: (1) enrolled patients with histologically confirmed breast cancer undergoing metastatic workup, (2) evaluated FDG-PET/CT and/or FDG-PET/MRI in comparison with at least one other imaging modality, (3) used a valid reference standard (e.g., biopsy, imaging follow-up, or clinical course), and (4) reported sufficient data to

calculate diagnostic accuracy outcomes. Studies were excluded if they lacked original patient data, were not full-text articles, or did not report usable diagnostic performance measures. In total, 31 studies were included in the full review. For the detection of bone metastases, Xia conducted separate meta-analyses using both patient-based and lesion-based 2x2 diagnostic accuracy data. To align with the scope of this guideline—which focuses on the value of imaging modalities for detecting oligometastases at the patient level—only the patient-based data were included in the current analysis.

For [$^{18}$F]FDG PET/CT, the patient-based meta-analysis included 6 studies with a total of 433 breast cancer patients, of whom 98 were diagnosed with bone metastases. For [$^{18}$F]FDG PET/MRI, the patient-based analysis included 3 studies with 343 patients, of whom 41 had bone metastases. Most studies were retrospective diagnostic accuracy cohorts. The populations, imaging indications, and comparator tests varied but were broadly consistent with the intended PICO.

Diagnostic accuracy measures (sensitivity, specificity, PPV, NPV) were pooled using bivariate meta-analysis. Hierarchical summary ROC curves were generated. Risk of bias was assessed with the QUADAS-2 tool and judged to be low across most domains. The review adhered to PRISMA guidelines and reported a reproducible search strategy.

Xia (2023) did not include analysis on NPV and PPV, but provides 2x2 table information. For the purpose of this review, bivariate meta-analysis (Reitsma model) was conducted in R using the mada package, with pooled sensitivity and specificity estimates obtained via logit-transformed random effects. Mean PPV and NPV were estimated across studies from observed 2×2 tables.

The evidence from Xia (2023) should be considered indirect for this question, since the included studies evaluated imaging modalities in the general context of metastatic breast cancer rather than specifically assessing the incremental value of MRI after a positive FDG-PET/CT in patients with suspected oligometastases. Furthermore, although the search included MRI of the spine, pelvis, and liver, the included studies provided quantitative accuracy data only for bone metastases. This narrows the evidence base relative to the intended scope of the review.

**Table 3. Characteristics of included studies in Xia 2023**

| Study | Participants | Comparison | Follow-up | Outcome measures | Comments | Risk of bias (per outcome measure)* |
|---|---|---|---|---|---|---|
| *Included in systematic review Xia, 2023* | | | | | | |
| Balci, 2012 Retrospective study | N=162 patients in the initial or post-treatment stage; evaluated with FDG-PET/CT. 49 (30%) with bone metastases. Location: Turkey. | Index: FDG-PET/CT; Reference: clinical/radiological follow-up. Single-arm cohort study. | ≥6 months | FDG-PET/CT: TP = 28, FP = 0, FN = 0, TN = 12, Sensitivity = 100.0%, Specificity = 100.0% | Study used visual assessment without explicit SUV cut-off. No funding/conflict issues reported. | Potential bias from lack of blinding and retrospective design. May overestimate specificity. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Mean age: 50. Previous treatment: Yes (surgery). | | | | | |
| Bruckmann, 2021 Prospective study | N=154 patients in the post-treatment stage; evaluated with FDG-PET/MRI. 7 (5%) had bone metastases. Location: Germany. Mean age: 53,8 (SD 11,9). Previous treatment: No. | Index: FDG-PET/MRI; Reference: follow-up and histopathology. Comparator: contrast-enhanced CT (head-to-head). | ≥6 months | FDG-PET/MRI: TP = 8, FP = 1, FN = 0, TN = 18, Sensitivity = 100.0%, Specificity = 94.7% | Head-to-head study. PET/MRI demonstrated superior lesion detection. No COI reported. | Low RoB, though small sample. |
| Botsikas, 2018 Prospective study | N=80 patients in the initial or post-treatment stage; evaluated with FDG-PET/CT and FDG-PET/MRI. 9 (11%) with bone metastases. Location: Switzerland. Median age: 48 (SD 12,9). Previous treatment: Unknown. | Index-1: FDG-PET/MRI; Index-2: FDG-PET/CT; Reference: biopsy or follow-up. Comparator: both modalities assessed. | ≥6 months | FDG-PET/CT: TP = 10, FP = 0, FN = 1, TN = 10, Sensitivity = 90.9%, Specificity = 100.0%; FDG-PET/MRI: TP = 10, FP = 0, FN = 1, TN = 10, Sensitivity = 90.9%, Specificity = 100.0% | Head-to-head modality comparison; emphasized improved lesion detection on MRI. No conflicts reported. | Low RoB. Minor concern over verification bias; authors note improved detection but small sample. |
| Catalano, 2015 | N=109 patients in | Index-1: FDG-PET/CT | ≥6 months | FDG-PET/CT: | Prospective design with | Low RoB. Good methodology, |

| | | | | | | |
|---|---|---|---|---|---|---|
| Prospecti ve study | the initial or post-treatment stage; evaluated with FDG-PET/CT and FDG-PET/MRI. 25 (23%) with bone metastase s. Location: Italy. Mean age: 58 (SD 10,7). Previous treatment: Yes (surgery). | Index-2: FDG-PET/MRI; Reference: biopsy/follow-up. Comparator: both modalities assessed. | | TP = 24, FP = 2, FN = 2, TN = 32, Sensitivity = 92.3%, Specificity = 94.1%; FDG-PET/MRI: TP = 24, FP = 1, FN = 2, TN = 33, Sensitivity = 92.3%, Specificity = 97.1% | direct head-to-head comparison. No industry funding. | small sample size limits generalizability. |
| Hahn, 2011 Retrospec tive study | N=29 patients in the initial stage; evaluated with FDG-PET/CT. 8 (28%) with bone metastase s. Location: Germany. Mean age: 58 (35-78). Previous treatment: Unknown. | Index: FDG-PET/CT; Reference: histopathology or follow-up. No comparator arm. | ≥6 months | FDG-PET/CT: TP = 24, FP = 0, FN = 1, TN = 15, Sensitivity = 96.0%, Specificity = 100.0% | Small cohort. Potential overestimation of sensitivity due to selection. No significant conflicts reported. | Potential bias from lack of blinding and retrospective design. Small sample bias; no pre-specified threshold; high sensitivity may not generalize. |
| Niikura, 2016 Retrospec tive study | N=28 patients in the initial or post-treatment stage; evaluated with FDG-PET/CT. 7(25%) with bone | Index: FDG-PET/CT; Reference: histopathology or follow-up. No comparator. | ≥6 months | FDG-PET/CT: TP = 40, FP = 4, FN = 4, TN = 28, Sensitivity = 90.9%, Specificity = 87.5% | Authors noted good accuracy, though CT component of PET/CT lacked contrast. No conflicts disclosed. | Potential bias from lack of blinding and retrospective design. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | metastases. Location: Japan. Median age: 59 (31-76). Previous treatment: Yes (surgery). | | | | | |
| Rager, 2018 Retrospective study | N=25 patients in the initial or post-treatment stage; evaluated with FDG-PET/CT. 12(48%) with bone metastases. Location: Switzerland. Median age: 61 (38-82). Previous treatment: Unknown. | Index: FDG-PET/CT; Reference: histopathology or follow-up. No comparator. | ≥6 months | FDG-PET/CT: TP = 16, FP = 0, FN = 0, TN = 5, Sensitivity = 100.0%, Specificity = 100.0% | Mixed cohort; no clear comparator arm. No conflicts of interest reported. | Potential bias from lack of blinding and retrospective design. |

*For further details, see risk of bias table in the appendix

Results

**Index 1: [18F]FDG PET/CT**

Xia (2023) included **6 studies** with a total of 433 **breast cancer patients** undergoing [18F]FDG PET/CT for detection of bone metastases, of whom 98 (23%) were diagnosed with bone metastases. Results are shown in table 4 and figure 1. Individual study estimates ranged from 67% to 100% for sensitivity, from 64% to 100% for specificity, from 87% to 100% for NPV and from 70% to 100% for PPV.

For the purpose of this review, bivariate meta-analysis (Reitsma model) was conducted in R using the mada package, with pooled sensitivity and specificity estimates obtained via logit-transformed random effects. Mean PPV and NPV were estimated across studies from observed 2×2 tables:

- Pooled Sensitivity: 0.96 (95% CI: 0.92–0.98)
- Pooled Specificity: 0.95 (95% CI: 0.91–0.97)
- Approximate Mean NPV: 0.95
- Approximate Mean PPV: 0.94

**Table 4**. Sensitivity, specificity, NPV and PPV for diagnosing metastasis in patients with breast cancer using [18F]FDG PET/CT (Xia 2023).

| Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Balci 2012 | 162 | 41 | 0 | 8 | 113 | 0.84 (0.70 – 0.93) | 1.00 (0.97 – 1.00) | 1.00 (0.89 – 1.00) | 0.93 (0.87 – 0.97) |
| Botsikas 2018 | 80 | 6 | 0 | 3 | 71 | 0.67 (0.30 – 0.93) | 1.00 (0.95 – 1.00) | 1.00 (0.52 – 1.00) | 0.96 (0.88 – 0.99) |
| Catalano 2015 | 109 | 22 | 1 | 3 | 83 | 0.88 (0.69 – 0.97) | 0.99 (0.94 – 1.00) | 0.96 (0.76 – 1.00) | 0.97 (0.89 – 0.99) |
| Hahn 2011 | 29 | 8 | 0 | 0 | 21 | 1.00 (0.63 – 1.00) | 1.00 (0.84 – 1.00) | 1.00 (0.60 – 1.00) | 1.00 (0.81 – 1.00) |
| Niikura 2016 | 28 | 7 | 3 | 0 | 18 | 1.00 (0.59 – 1.00) | 0.86 (0.64 – 0.97) | 0.70 (0.35 – 0.92) | 1.00 (0.78 – 1.00) |
| Rager 2018 | 25 | 10 | 0 | 2 | 13 | 0.83 (0.52 – 0.98) | 1.00 (0.75 – 1.00) | 1.00 (0.66 – 1.00) | 0.87 (0.58 – 0.98) |

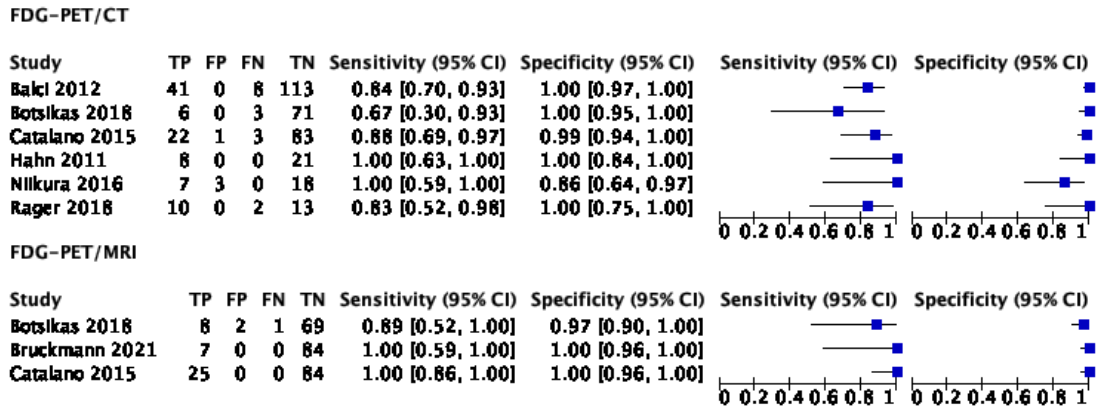


**Figure 1** Forest plot of [18F]FDG PET/CT and [18F]FDG PET/MRI for detecting bone metastasis in breast cancer patients (Zhang 2014). Plot shows study-specific estimates of sensitivity and specificity (squares) with 95% confidence interval (black line) and study. TP: true positive; FP: false positive; FN: false negative; TN: true negative; CI = confidence interval.

**Index 2: [18F]FDG PET/MRI**

Xia (2023) included **3 studies** with a total of 343 **breast cancer patients** undergoing [18F]FDG PET/MRI for detection of bone metastases, of whom 41 (12%) were diagnosed with bone metastases. Results are shown in table 5 and figure 1. Individual study estimates ranged from 89% to 100% for sensitivity, from 97% to 100% for specificity, from 99% to 100% for NPV and from 80% to 100% for PPV.

For the purpose of this review, bivariate meta-analysis (Reitsma model) was conducted in R using the mada package, with pooled sensitivity and specificity estimates obtained via logit-transformed random effects. Mean PPV and NPV were estimated across studies from observed 2×2 tables:

- Pooled Sensitivity: 0.93 (95% CI: 0.74–0.99)
- Pooled Specificity: 0.99 (95% CI: 0.94–1)
- Approximate Mean NPV: 1
- Approximate Mean PPV: 0.93

**Table 5**. Sensitivity, specificity, NPV and PPV for diagnosing metastasis in patients with breast cancer using [18F]FDG PET/MRI (Xia 2023).

| Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Botsikas 2018 | 80 | 8 | 2 | 1 | 69 | 0.89 (0.52 – 1.00) | 0.97 (0.90 – 1.00) | 0.80 (0.44 – 0.96) | 0.99 (0.91 – 1.00) |
| Bruckmann 2021 | 154 | 7 | 0 | 0 | 147 | 1.00 (0.59 – 1.00) | 1.00 (0.96 – 1.00) | 1.00 (0.56 – 1.00) | 1.00 (0.97 – 1.00) |
| Catalano 2015 | 109 | 25 | 0 | 0 | 84 | 1.00 (0.86 – 1.00) | 1.00 (0.96 – 1.00) | 1.00 (0.83 – 1.00) | 1.00 (0.95 – 1.00) |

**Index 3: Contrast-Enhanced CT (CECT) and/or Bone Scintigraphy (BS)**
CT and BS were included only as comparator modalities in several of the FDG PET/CT studies. Xia (2023) did not conduct pooled analyses of sensitivity or specificity for CT or BS alone. Therefore, no diagnostic accuracy data are available specifically for these tests in this review.

**Index 4: Whole-body MRI or targeted MRI (spine, pelvis, liver)**
MRI was included only as comparator in several of the FDG PET/MRI studies. Xia (2023) did not conduct pooled analyses of sensitivity or specificity for MRI alone. Therefore, no diagnostic accuracy data are available specifically for these tests in this review.

Summary of Findings

**Summary of Findings: Targeted MRI (spine, pelvis, liver) after positive FDG-PET/CT to diagnose (oligo)metastasis in patients with breast cancer**

Population: Patients with breast cancer and a positive FDG-PET/CT with suspected (oligo)metastases
Intervention: Targeted MRI (spine, pelvis, liver) after FDG PET/CT
Comparator: FDG PET/CT alone
Reference: Pathological anatomical (PA) diagnosis or clinical diagnosis.

| **Outcome** | **Study results and measurements** | **FDG-PET/CT alone (Xia 2023, 6 studies; N=433, 98 events)** | **MRI after PET/CT (proxy from PET/MRI, Xia 2023, 3 studies; N=343, 41 events)** | **Certainty of the Evidence** (Quality of evidence) | **Conclusions** |
|---|---|---|---|---|---|
| Sensitivity (critical) | The systematic review and meta-analysis of Xia (2023) 6 studies with a total of 433 breast cancer patients undergoing [18F]FDG PET/CT for detection of bone metastases, of whom 98 (23%) were diagnosed with bone metastases. Xia (2023) also included 3 studies with a total of 343 breast cancer patients undergoing [18F]FDG | 0.96 (95% CI: 0.92–0.98) | 0.93 (95% CI: 0.74–0.99) | **Very low** Due to serious risk of bias, due to indirectness[1,2] | [18F]FDG PET/MRI may have higher sensitivity and similar specificity compared to [18F] FDG PET/CET in diagnosing bone (oligo)metastasis in patients with breast cancer, but evidence is indirect for the sequential setting after a positive PET/CT.<br><br>*(Xia, 2023)* |
| Specificity (important) | | 0.95 (95% CI: 0.91–0.97) | 0.99 (95% CI: 0.94–1) | **Very low** Due to serious risk of bias, due to indirectness [1,2] | |
| Negative predictive value (critical) | | Approximate Mean: 0.95 | Approximate Mean: 1 | **Very low** Due to serious risk of bias, due to indirectness, indirect estimate [1,3] | |
| Positive predictive value (important) | | Approximate Mean PPV: 0.9 | Approximate Mean PPV: 0.93 | **Very low** Due to serious risk of bias, due to indirectness indirect estimate [1,3] | |

| | | | | | |
|---|---|---|---|---|---|
| | PET/MRI for detection of bone metastases, of whom 41 (12%) were diagnosed with bone metastases. | | | | |

The body of evidence consists entirely of diagnostic accuracy studies in breast cancer patients with bone metastases. Although the search strategy covered MRI of the spine, pelvis, and liver, the available data were limited to bone metastases. This restricts applicability and introduces indirectness regarding both the disease setting and the anatomical scope. Most studies were retrospective cohorts, increasing the risk of selection and verification bias. None stratified outcomes for oligometastatic versus polymetastatic disease or assessed sequential MRI after positive FDG-PET/CT.

Downgraded for imprecision: small number of studies and wide confidence intervals.

NPV and PPV were derived using mean-based approximations from study-level data and are considered indirect estimates.

**Kennisvragen**

Tijdens de ontwikkeling van deze module is systematisch naar onderzoeken gezocht die de zoekvraag kunnen beantwoorden. Door gebruik te maken van een systematische literatuuranalyse met beoordeling van de bewijskracht is duidelijk geworden dat er binnen deze module nog kennisvragen bestaan. Het cluster meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag 1

Wat is de aanvullende waarde van MRI (wervelkolom, bekken of lever) ná een positieve FDG-PET/CT bij patiënten met borstkanker en verdenking op oligometastasen, in vergelijking met FDG-PET/CT alleen, voor het detecteren van aanvullende metastasen en het verbeteren van behandeluitkomsten?

Toelichting: Dit is de huidige uitgangsvraag. Er ontbreekt volledig direct bewijs. Prospectief diagnostisch onderzoek is noodzakelijk omdat de uitkomst direct de behandelstrategie beïnvloedt (curatief vs. palliatief). Zie hiervoor ook de uitgebreide trialsuggesties in het artikel van Delphi European expert panel consensus (Pasquier 2023).

Kennisvraag 2

Wat is de klinische impact van nieuwe PET-tracers (zoals FES, NaF, FAPI, PSMA of Fluciclovine) bij borstkanker op het bevestigen van oligometastasen of oligoprogressie, vergeleken met FDG-PET/CT?

Toelichting: Nieuwe tracers worden al onderzocht en kunnen potentieel de diagnostische standaard veranderen. Onderzoek met harde klinische eindpunten (behandelkeuze, overleving) is dringend nodig.

Kennisvraag 3

Wat is de kosteneffectiviteit van aanvullende MRI na FDG-PET/CT of van nieuwe PET-tracers bij borstkanker, in vergelijking met standaard FDG-PET/CT, voor de detectie van oligometastasen?

Toelichting: Kosten en capaciteit zijn belangrijke belemmeringen voor implementatie. Kosteneffectiviteitsonderzoek is cruciaal voor beleid, maar kan pas goed worden uitgevoerd nadat er meer gegevens zijn over diagnostische waarde en klinische impact.

Kennisvraag 4

Welke patiëntsubgroepen met borstkanker en oligometastasen profiteren het meest van aanvullende beeldvorming (MRI of nieuwe PET-tracers) na FDG-PET/CT?
Toelichting: Dit is relevant voor gepersonaliseerde zorg, maar vereist eerst robuuste basisgegevens uit bredere studies. Subgroepanalyses kunnen in vervolgonderzoek worden ingebouwd zodra er voldoende grotere prospectieve cohorten beschikbaar zijn.

**Implementeren-tabel**

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

***Implementatietabel***

| ***Vraag*** | ***Antwoord:*** *Kruis aan en licht toe/ beschrijf* | | ***Toelichting keuze:*** |
|---|---|---|---|
| **I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?** | **x** | **Ongewenste praktijkvariatie** | |
| | | **Nieuwe evidentie** | |
| | | **Anders** | |
| **I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?** | | **< 1000** | |
| | **X** | **< 5000** | |
| | | **5000-40.000** | |
| | | **> 40.000** | |
| **I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?** | | **Ja** | |
| | **x** | **Nee** | |
| **I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:** | | **Belemmerende factoren** | **Bevorderende factoren/ kansen** |
| **Richtlijn/ klinisch traject (innovatie)** | | Onzeker bewijs voor aanvullende MRI<br>MRI capaciteit | Mogelijk meer zekerheid over oligosetting na aanvullende MRI-scan |
| **Zorgverleners (artsen en verpleegkundigen)** | | personeelscapaciteit | |
| **Patiënt/ cliënt (naasten)** | | Toevalsbevindingen met mogelijk meer onzekerheid | |
| **Sociale context** | | | |
| **Organisatorische context** | | capaciteit | |

| | | | |
|---|---|---|---|
| **Financiële en juridische context** | | | |
| **I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)**<br><br>**B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.* | | **A** | **B** |
| | | Patiënt/ cliënt (naaste) | |
| | **x** | Professional | Kennis nemen richtlijn |
| | **x** | Beroepsvereniging, nl | Richtlijn verspreiden, onder aandacht. |
| | | Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ) | |
| | | Zorgverzekeraars/ NZa | |
| | | Zorginstituut [duiding nodig] | |
| | | Anders | |
| **I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?** | **x** | < 1 jaar | |
| | | binnen 2-3 jaar | |
| **I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling?**<br>*De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.* | | Ja | |
| | **x** | Nee | Alleen bekendheid bij de behandelaars met de richtlijn. Aanbeveling richt zich op het niet standaard maken van extra beeldvorming. |
| **I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst.**<br>*Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.* | | Ja * | |
| | **x** | Nee | |

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de*

*implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

## 5 Risk of Bias tables

*Table of quality assessment for systematic reviews of diagnostic studies*
*Research question: What is the diagnostic test accuracy of scan modalities for detecting oligometastasis in breast cancer patients?*

| Study<br><br>First author, year | Appropriate and clearly focused question?[1]<br><br>Yes/no/unclear | Comprehensive and systematic literature search?[2]<br><br>Yes/no/unclear | Description of included and excluded studies?[3]<br><br>Yes/no/unclear | Description of relevant characteristics of included studies?[4]<br><br>Yes/no/unclear | Assessment of scientific quality of included studies?[5]<br><br>Yes/no/unclear | Enough similarities between studies to make combining them reasonable?[6]<br><br>Yes/no/unclear | Potential risk of publication bias taken into account?[7]<br><br>Yes/no/unclear | Potential conflicts of interest reported?[8]<br><br>Yes/no/unclear |
|---|---|---|---|---|---|---|---|---|
| Xia, 2023 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |

*Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)*
*Research question: What is the diagnostic test accuracy of scan modalities for detecting oligometastasis in breast cancer patients?*

| Study reference | Patient selection | Index test | Reference standard | Flow and timing | Comments with respect to applicability |
|---|---|---|---|---|---|
| Balci 2012 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid inappropriate exclusions? Yes<br>CONCLUSION: Could the selection of patients have introduced bias? RISK: LOW | Were the index test results interpreted without knowledge of the results of the reference standard? Yes<br>Was the index test conducted in a manner consistent with clinical practice? Yes<br>CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? RISK: LOW | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the reference standard results interpreted without knowledge of the index test? Yes<br>CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW | Was there an appropriate interval between index test and reference standard? Yes<br>Did all patients receive the same reference standard? Yes<br>Were all patients included in the analysis? Yes<br>CONCLUSION: Could the patient flow have introduced bias? RISK: LOW | Were there concerns that the included patients do not match the review question? No<br>Were there concerns that the index test, its conduct, or interpretation differ from the review question? No<br>Were there concerns that the target condition as defined by the reference standard does not match the question? No |

| Study reference | Patient selection | Index test | Reference standard | Flow and timing | Comments with respect to applicability |
|---|---|---|---|---|---|
| Bruckmann 2021 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid inappropriate exclusions? Yes<br>CONCLUSION: Could the selection of patients have introduced bias?<br>RISK: LOW | Were the index test results interpreted without knowledge of the results of the reference standard? Yes<br>Was the index test conducted in a manner consistent with clinical practice? Yes<br>CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?<br>RISK: LOW | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the reference standard results interpreted without knowledge of the index test? Yes<br>CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?<br>RISK: LOW | Was there an appropriate interval between index test and reference standard? Yes<br>Did all patients receive the same reference standard? Yes<br>Were all patients included in the analysis? Yes<br>CONCLUSION: Could the patient flow have introduced bias?<br>RISK: LOW | Were there concerns that the included patients do not match the review question? No<br>Were there concerns that the index test, its conduct, or interpretation differ from the review question? No<br>Were there concerns that the target condition as defined by the reference standard does not match the question? No |
| Botsikas 2018 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid inappropriate exclusions? Yes<br>CONCLUSION: Could the selection of patients have introduced bias?<br>RISK: LOW | Were the index test results interpreted without knowledge of the results of the reference standard? Yes<br>Was the index test conducted in a manner consistent with clinical practice? Yes<br>CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?<br>RISK: LOW | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the reference standard results interpreted without knowledge of the index test? Yes<br>CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?<br>RISK: LOW | Was there an appropriate interval between index test and reference standard? Yes<br>Did all patients receive the same reference standard? Yes<br>Were all patients included in the analysis? Yes<br>CONCLUSION: Could the patient flow have introduced bias?<br>RISK: LOW | Were there concerns that the included patients do not match the review question? No<br>Were there concerns that the index test, its conduct, or interpretation differ from the review question? No<br>Were there concerns that the target condition as defined by the reference standard does not match the question? No |
| Catalano 2015 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid | Were the index test results interpreted without knowledge of the results of the | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the | Was there an appropriate interval between index test and reference standard? Yes | Were there concerns that the included patients do not match the review question? No |

| Study reference | Patient selection | Index test | Reference standard | Flow and timing | Comments with respect to applicability |
|---|---|---|---|---|---|
| | inappropriate exclusions? Yes<br>CONCLUSION: Could the selection of patients have introduced bias?<br>RISK: LOW | reference standard? Yes<br>Was the index test conducted in a manner consistent with clinical practice? Yes<br>CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?<br>RISK: LOW | reference standard results interpreted without knowledge of the index test? Yes<br>CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?<br>RISK: Unclear | Did all patients receive the same reference standard? Yes<br>Were all patients included in the analysis? Yes<br>CONCLUSION: Could the patient flow have introduced bias?<br>RISK: LOW | Were there concerns that the index test, its conduct, or interpretation differ from the review question? No<br>Were there concerns that the target condition as defined by the reference standard does not match the question? No |
| Hahn 2011 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid inappropriate exclusions? Yes<br>CONCLUSION: Could the selection of patients have introduced bias?<br>RISK: LOW | Were the index test results interpreted without knowledge of the results of the reference standard? Yes<br>Was the index test conducted in a manner consistent with clinical practice? Yes<br>CONCLUSION: Could the conduct or interpretation of the index test have introduced bias?<br>RISK: HIGH No pre-specified cut-off for index test, potentially introducing bias. | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the reference standard results interpreted without knowledge of the index test? Yes<br>CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias?<br>RISK: LOW | Was there an appropriate interval between index test and reference standard? Yes<br>Did all patients receive the same reference standard? Yes<br>Were all patients included in the analysis? Yes<br>CONCLUSION: Could the patient flow have introduced bias?<br>RISK: LOW | Were there concerns that the included patients do not match the review question? No<br>Were there concerns that the index test, its conduct, or interpretation differ from the review question? No<br>Were there concerns that the target condition as defined by the reference standard does not match the question? No |
| Niikura 2016 | Was a consecutive or random sample of patients enrolled? Yes<br>Did the study avoid inappropriate exclusions? Yes<br>CONCLUSION: | Were the index test results interpreted without knowledge of the results of the reference standard? Yes<br>Was the index test | Is the reference standard likely to correctly classify the target condition? Yes<br>Were the reference standard results interpreted without | Was there an appropriate interval between index test and reference standard? Yes<br>Did all patients receive the same reference | Were there concerns that the included patients do not match the review question? No<br>Were there concerns that the index test, its |

| Study reference | Patient selection | Index test | Reference standard | Flow and timing | Comments with respect to applicability |
|---|---|---|---|---|---|
| | Could the selection of patients have introduced bias? RISK: LOW | conducted in a manner consistent with clinical practice? Yes CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? RISK: LOW | knowledge of the index test? Yes CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW | standard? Yes Were all patients included in the analysis? Yes CONCLUSION: Could the patient flow have introduced bias? RISK: LOW | conduct, or interpretation differ from the review question? No Were there concerns that the target condition as defined by the reference standard does not match the question? No |
| Rager 2018 | Was a consecutive or random sample of patients enrolled? Yes Did the study avoid inappropriate exclusions? Yes CONCLUSION: Could the selection of patients have introduced bias? RISK: LOW | Were the index test results interpreted without knowledge of the results of the reference standard? Yes Was the index test conducted in a manner consistent with clinical practice? Yes CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? RISK: LOW | Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the index test? Yes CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW | Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes CONCLUSION: Could the patient flow have introduced bias? RISK: LOW | Were there concerns that the included patients do not match the review question? No Were there concerns that the index test, its conduct, or interpretation differ from the review question? No Were there concerns that the target condition as defined by the reference standard does not match the question? No |

**Table of excluded studies**

| Reference | Reason for exclusion |
|---|---|
| Ali Abdulhasan Kadhim, Peyman Sheikhzadeh, Mehrshad Abbasi, Nasim Vahidfar, Saeed Afshar, Mohsen Bakhshi Kashi, Negisa Seyyedi, & Mohammad Reza Ay. (2023). FEASIBILITY OF [64CU]CU-TRASTUZUMAB PET/CT IMAGING IN BREAST CANCER: A SYSTEMATIC REVIEW. Journal of Population Therapeutics and Clinical Pharmacology, 30(17), 2375-2385. https://doi.org/10.53555/jptcp.v30i17.2999 | wrong population (subpopulation HER2 breast cancer); wrong search strategy, at high risk of missing relevant references |
| Chang WY, Tseng NC, Chen LY, Chang CW, Huang YY, Huang YT, Ou YC, Peng NJ. Comparison of the Detection Performance Between FAP and FDG PET/CT | wrong population (not breast cancer specific) |

| | |
|---|---|
| in Various Cancers: A Systemic Review and Meta-analysis. Clin Nucl Med. 2023 Feb 1;48(2):132-142. doi: 10.1097/RLU.0000000000004438. Epub 2022 Oct 26. PMID: 36607362. | |
| Dall' Armellina S, Aghakhanyan G, Rizzo A, Fanni SC, Aringhieri G, Faggioni L, Cioni D, Neri E, Volterrani D, Morbelli S. PSMA-targeted PET imaging for brain metastases from non-prostatic solid tumors: a systematic review. Front Oncol. 2025 Mar 17;15:1553505. doi: 10.3389/fonc.2025.1553505. PMID: 40165900; PMCID: PMC11955466. | wrong population (not breast cancer specific); wrong publication type (no analysis diagnostic accuracy) |
| Evangelista L., Cuppari L., Burei M., Zorz A., Caumo F.. Head-to-head comparison between 18F-FDG PET/CT and PET/MRI in breast cancer. Clin Transl Imaging 7, 99–104 (2019). https://doi.org/10.1007/s40336-019-00319-2 | Study lacks a systematic review methodology and insufficient search strategy to identify all relevant breast cancer diagnostic accuracy studies. |
| Gerke O, Naghavi-Behzad M, Nygaard ST, Sigaroudi VR, Vogsen M, Vach W, Hildebrandt MG. Diagnosing Bone Metastases in Breast Cancer: A Systematic Review and Network Meta-Analysis on Diagnostic Test Accuracy Studies of 2-[18F]FDG-PET/CT, 18F-NaF-PET/CT, MRI, Contrast-Enhanced CT, and Bone Scintigraphy. Semin Nucl Med. 2025 Jan;55(1):137-151. doi: 10.1053/j.semnuclmed.2024.10.008. Epub 2024 Nov 14. PMID: 39547916. | Incomplete search strategy; at risk of missing key imaging modalities and studies |
| Harlianto NI, van der Star S, Suelmann BBM, de Jong PA, Verlaan JJ, Foppen W. Diagnostic accuracy of imaging modalities for detection of spinal metastases: a systematic review and meta-analysis. Clin Transl Oncol. 2025 May;27(5):2316-2326. doi: 10.1007/s12094-024-03765-1. Epub 2024 Oct 29. PMID: 39470945; PMCID: PMC12033096. | wrong population (not breast cancer specific); wrong outcome (not reported per study, also no 2x2 data available) |
| Hu H, Hu X, Liang Z, Yang W, Li S, Li D, Cai J. Diagnostic performance of 18F-FDG PET/CT vs. 18F-NaF PET/CT in breast cancer with bone metastases: An indirect comparative meta-analysis. Oncol Lett. 2024 Sep 12;28(5):546. doi: 10.3892/ol.2024.14679. PMID: 39319212; PMCID: PMC11420642. | wrong search strategy, wrong comparison |
| Kurland BF, Wiggins JR, Coche A, Fontan C, Bouvet Y, Webner P, Divgi C, Linden HM. Whole-Body Characterization of Estrogen Receptor Status in Metastatic Breast Cancer with 16α-18F-Fluoro-17β-Estradiol Positron Emission Tomography: Meta-Analysis and Recommendations for Integration into Clinical Applications. Oncologist. 2020 Oct;25(10):835-844. doi: 10.1634/theoncologist.2019-0967. Epub 2020 May 15. PMID: 32374053; PMCID: PMC7543360. | wrong population (subpopulation HER2 borstkanker); wrong search strategy; wrong outcome |
| Lu XR, Qu MM, Zhai YN, Feng W, Gao Y, Lei JQ. Diagnostic role of 18F-FDG PET/MRI in the TNM staging of breast cancer: a systematic review and meta-analysis. Ann Palliat Med. 2021 Apr;10(4):4328- | wrong search strategy |

| | |
|---|---|
| 4337. doi: 10.21037/apm-20-2555. Epub 2021 Apr 12. PMID: 33894709. | |
| Mirshahvalad SA, Kohan A, Metser U, Hinzpeter R, Ortega C, Farag A, Veit-Haibach P. Diagnostic performance of whole-body [18F]FDG PET/MR in cancer M staging: A systematic review and meta-analysis. Eur Radiol. 2024 Jan;34(1):673-685. doi: 10.1007/s00330-023-10009-3. Epub 2023 Aug 3. PMID: 37535156. | wrong population (not breast cancer specific) |
| Mo JA. Safety and Effectiveness of F-18 Fluoroestradiol Positron Emission Tomography/Computed Tomography: a Systematic Review and Meta-analysis. J Korean Med Sci. 2021 Nov 1;36(42):e271. doi: 10.3346/jkms.2021.36.e271. PMID: 34725978; PMCID: PMC8560320. | wrong population (subpopulatie HER2 borstkanker); wrong search strategy |
| Rong Y, Ren H, Ding X. MRI and Bone Scintigraphy for Breast Cancer Bone Metastase: A Meta-analysis. Open Med (Wars). 2019 Mar 13;14:317-323. doi: 10.1515/med-2019-0029. PMID: 30931397; PMCID: PMC6434664. | wrong search strategy |
| Ruan D, Sun L. Diagnostic Performance of PET/MRI in Breast Cancer: A Systematic Review and Bayesian Bivariate Meta-analysis. Clin Breast Cancer. 2023 Feb;23(2):108-124. doi: 10.1016/j.clbc.2022.11.010. Epub 2022 Dec 1. PMID: 36549970. | wrong population (not breast cancer specific) |
| Shen F, Liu Q, Wang Y, Chen C, Ma H. Comparison of [18F] FDG PET/CT and [18F]FDG PET/MRI in the Detection of Distant Metastases in Breast Cancer: A Meta-Analysis. Clin Breast Cancer. 2025 Feb;25(2):e113-e123.e4. doi: 10.1016/j.clbc.2024.09.015. Epub 2024 Sep 28. PMID: 39438190. | Search too narrow and at high risk of missing relevant studies |
| Wass G, Clifford K, Subramaniam RM. Evaluation of the Diagnostic Accuracy of FAPI PET/CT in Oncologic Studies: Systematic Review and Metaanalysis. J Nucl Med. 2023 Aug;64(8):1218-1224. doi: 10.2967/jnumed.123.265471. Epub 2023 Jun 8. PMID: 37290798. | wrong comparison (not CT or MRI); wrong population (not breast cancer specific) |
| Zamanian M, Treglia G, Abedi I. Diagnostic Accuracy of PET with Different Radiotracers versus Bone Scintigraphy for Detecting Bone Metastases of Breast Cancer: A Systematic Review and a Meta-Analysis. J Imaging. 2023 Dec 8;9(12):274. doi: 10.3390/jimaging9120274. PMID: 38132692; PMCID: PMC10744045. | Search too narrow and at high risk of missing relevant studies |
| Zhang C, Liang Z, Liu W, Zeng X, Mo Y. Comparison of whole-body 18F-FDG PET/CT and PET/MRI for distant metastases in patients with malignant tumors: a meta-analysis. BMC Cancer. 2023 Jan 10;23(1):37. doi: 10.1186/s12885-022-10493-8. PMID: 36624425; PMCID: PMC9830828. | wrong outcome (distant metastasis); wrong search strategy |

| | |
|---|---|
| Zhang J., Xiong J., Wang M., Wu B, Zhang C. Comparison of the diagnostic value of 68Ga-FAPI and 18F-FDG PET/CT in breast cancer: a systematic review. Clin Transl Imaging 12, 787–798 (2024). https://doi.org/10.1007/s40336-024-00656-x | wrong comparison (not CT or MRI) |

**Literature search strategy**

***Algemene informatie***

| | |
|---|---|
| Cluster/richtlijn:NIV - Borstkanker | |
| Uitgangsvraag/modules: Wat is de waarde van beeldvormingsmodaliteiten in de diagnostiek van oligometastasen bij borstkanker? | |
| Database(s): Embase.com, Ovid/Medline | Datum: 26-5-2025 |
| Periode: vanaf 2019 | Talen: geen restrictie |
| Literatuurspecialist: Ingeborg van Dusseldorp | Rayyan review: https://new.rayyan.ai/reviews/1471365/screening |
| Te gebruiken voor richtlijntekst:<br>A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2019 to 26-5-2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from the following primary search concepts: (1) Metastasis OR oligometastases, (2) MRI OR FDG-PET, MRI, FES-PET, FAPI-PET OR 4-fase-CT, (3) Breast cancer. Duplicates were removed using EndNote software. After deduplication a total of 1260 records were imported for title/abstract screening | |

5 ***Zoekopbrengst***

| | **EMBASE** | **OVID/MEDLINE** | **Ontdubbeld** |
|---|---|---|---|
| SR | 101 | 43 | 107 |
| RCT | 290 | 104 | 306 |
| Observationele studies | 778 | 360 | 847 |
| **Totaal** | 1139 | 507 | **1260** |

****in Rayyan***

***Zoekstrategie***

**Embase.com**

| No. | Query | Results |
|---|---|---|
| #1 | 'metastasis'/exp/mj OR 'metastatic breast cancer'/exp OR 'oligometastasis'/exp OR 'oligometastatic disease'/exp OR 'oligometastatic breast cancer'/exp OR 'oligometastatic cancer'/exp OR 'oligoprogressive disease'/exp OR 'oligometastatic prostate cancer'/exp OR 'oligometastatic non small cell lung cancer'/exp OR 'oligometastatic colorectal cancer'/exp OR 'oligometastatic hormone sensitive prostate cancer'/exp OR 'oligometastatic lung cancer'/exp OR oligometasta*:ti,ab,kw OR 'oligo metasta*':ti,ab,kw OR oligorecur*:ti,ab,kw OR 'oligo recurr*':ti,ab,kw OR oligoprogres*:ti,ab,kw OR 'oligo progres*':ti,ab,kw OR oligoresidual*:ti,ab,kw OR 'oligo residual*':ti,ab,kw OR (((oligo* OR 'low burden' OR micro OR restricted OR minimal OR isolat* OR early OR distant OR 'low volume' OR local OR sparse OR few OR limited OR breast OR mamma) NEAR/6 metasta*):ti,ab,kw) | 499728 |
| #2 | 'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/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 'mr imag*':ti,ab,kw 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 OR rsfmri:ti,ab,kw | 1757977 |
| #3 | 'fluorodeoxyglucose'/exp OR 'fluoroestradiol f 18'/exp OR 'fluorodeoxyglucose f 18'/exp OR 'sodium fluoride f 18'/exp OR 'positron emission tomography'/exp OR 'single photon emission computed tomography'/exp OR fluorodeoxyglucose:ti,ab,kw OR 'fluoroestradiol f18':ti,ab,kw OR 'sodium fluoride f18':ti,ab,kw OR spect:ti,ab,kw OR petscan*:ti,ab,kw OR pet:ti,ab,kw OR petct:ti,ab,kw OR (((emission OR positron) NEAR/3 tomograph*):ti,ab,kw) OR radionuclid*:ti,ab,kw OR 'four dimensional computed tomography'/exp OR 'psma*':ti,ab,kw OR '4-fase-ct':ti,ab,kw | 525478 |
| #4 | 'breast cancer'/exp OR ((breast NEAR/3 (cancer* OR neoplasm* OR malignan* OR onco* OR carcinom* OR carcinogen* OR malignan*)):ti,ab,kw) | 796944 |
| #5 | #1 AND (#2 OR #3) AND #4 | 9463 |
| #6 | 'sensitivity and specificity'/de OR sensitivity:ab,ti OR specificity: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 OR (((false OR | 7023724 |

| | | |
|---|---|---|
| | true) NEAR/3 (negative OR positive)):ti,ab) OR 'area under the curve'/exp | |
| #7 | #5 AND #6 | 5883 |
| #8 | 'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw | 1116462 |
| #9 | 'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'randomization'/de OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ti,ab OR ((random* NEAR/2 (trial OR study)):ti,ab) OR ((random* NEAR/10 (trial OR trail OR 'clinical trial' OR 'clinical trail' OR 'clinical study' OR 'multicenter study' OR crossover OR 'cross over')):ti) OR (((randomised OR randomized) NEXT/6 study):ti) OR 'random* control* clinical trial':ti,ab OR 'random* control* clinical trail':ti,ab OR 'random* control* clinical study':ti,ab OR ((('single blind*' OR 'double blind*' OR 'triple blind*' OR 'quadruple blind*') NEAR/4 (study OR trial OR trail OR design)):ti,ab) OR placebo*:ti,ab OR randomly:ti,ab OR ((random* NEAR/3 distribut* NEAR/7 group*):ti,ab) OR (((pragmatic OR practical) NEXT/1 ('clinical trial' OR 'clinical trail')):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEXT/3 (trial OR trail)):ti,ab) OR ((random* NEAR/4 ('cross over*' OR crossover*)):ti,ab) OR ((phase NEAR/5 ('clinical trial' OR 'clinical trail' OR randomized OR randomised)):ti) OR ((random* NEAR/3 phase NEAR/3 (trial OR trail OR study)):ti,ab) | 3867561 |
| #10 | 'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de | 18358966 |

| | | |
|---|---|---|
| | 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 ((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) 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 (('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 | #7 AND [2019-2025]/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) | 1398 |
| #12 | #8 AND #11 | 101 |
| #13 | #9 AND #11 NOT #12 | 290 |
| #14 | #10 AND #11 NOT #12 NOT #13 | 778 |
| #15 | #12 OR #13 OR #14 | 1169 |
| #16 | 'radiolabelled psma pet/ct in breast cancer. a systematic review':ti | 1 |
| #17 | 'diagnosing bone metastases in breast cancer: a systematic review and network meta-analysis on diagnostic test accuracy studies':ti | 1 |
| #18 | #16 OR #17 | 2 |
| #19 | #15 AND #18 | 1 |

# Bijlagen bij module 9.2.3 Lokale behandeling locoregionale recidieven

**Background**

Regional recurrence of breast cancer refers to the return of the disease in the ipsi lateral regional lymph nodes after initial curative treatment (Kuo, 2008). While advances in treatment have significantly reduced recurrence rates, regional recurrences still present a clinical challenge due to their association with an increased risk of distant metastases.
Patients may present with symptoms of a regional recurrence: many patients present with palpable adenopathy in the axilla or supraclavicular fossa, although a regional recurrence may also present as a new onset of brachial plexopathy or lymphedema of the arm. These may occur in the absence of palpable adenopathy.
Solitary "sternal metastases" may actually represent direct extension of involved internal mammary nodes.
Optimal local treatment, including surgical approaches such as axillary lymph node dissection or local excision, as well as radiotherapy, remains a topic of debate.

Regional recurrence of breast cancer refers to the reappearance of disease in the ipsilateral regional lymph nodes (axillary, supraclavicular, infraclavicular, or parasternal) after initial curative treatment. In this guideline, “regional” refers exclusively to ipsilateral disease; contralateral or distant lymph node involvement is considered metastatic (M1). In the literature, definitions and staging of regional recurrence vary. In particular, ipsilateral supraclavicular lymph node involvement has historically been classified either as locoregional disease (N3c) or as metastatic disease (M1), depending on the TNM edition and study design. This inconsistency complicates comparison of outcomes across studies and may contribute to variability in reported prognosis and treatment approaches.

Although advances in systemic therapy, surgery, and radiotherapy have considerably reduced the incidence of regional recurrences, they continue to pose a clinical challenge because of their association with an increased risk of distant metastases and the complexity of prior treatments.

Patients may present with palpable lymphadenopathy in the axilla or supraclavicular fossa, but regional recurrence can also manifest as new-onset brachial plexopathy or arm lymphedema in the absence of palpable nodes. In some cases, solitary sternal lesions represent direct extension from involved internal mammary nodes rather than distant metastasis.

The optimal local management of regional recurrence remains uncertain and varies in clinical practice. Potential treatment options include surgical resection, radiotherapy, and systemic therapy—individually or in combination—depending on technical feasibility, prior treatments, and disease extent. A multidisciplinary approach is essential to balance the goals of durable local control, symptom relief, and prevention of distant progression while minimizing treatment-related morbidity.

For this module, a systematic literature search was performed to address two key questions: (1) the comparative effectiveness of surgery versus radiotherapy, and (2) the added value of combining these modalities in patients with regional recurrence of breast cancer without distant metastases. Other topics, including the potential role of the MARI procedure for axillary recurrence after systemic therapy, were not specifically covered by the search strategy and are therefore discussed qualitatively, drawing on existing evidence from related modules (particularly module 6.4.4.1) and expert consensus.

By focusing on the two most widely applicable and evidence-rich questions (PICO 1 and 2), the search ensured feasibility and targeted the clinical issues most likely to inform current practice, while still providing qualitative guidance for emerging procedures such as MARI.

**Search and select**

A systematic review of the literature was performed to answer the following questions: What are the (un)beneficial effects of surgical resection on overall survival, locoregional control, disease-free survival, morbidity (e.g. toxicity, side effects), and quality of life compared to radiotherapy in patients with breast cancer with a regional recurrence and without distant metastases?

**Table 1. PICO: Surgical effectiveness**

| | |
|---|---|
| Patients | Patients with breast cancer with a regional recurrence (axillary, periclavicular, or parasternal), without distant metastases |
| Intervention | Surgical resection |
| Control | Radiotherapy |
| Outcomes | Overall survival, locoregional control, disease-free survival, morbidity (e.g. toxicity, side effects), quality of life |
| Other selection criteria | Study design: systematic reviews and randomized controlled trials |

What are the (un)beneficial effects of a combined treatment (i.e. surgical resection with radiotherapy) on overall survival, locoregional control, disease-free survival, morbidity (e.g. toxicity, side effects), quality of life when compared to monotherapy (i.e. surgical resection only or radiotherapy only) in patients with breast cancer with a regional recurrence and without distant metastases?

**Table 2. PICO 2: Added value of combined treatment**

| | |
|---|---|
| Patients | Patients with breast cancer with a regional recurrence (axillary, periclavicular, or parasternal), without distant metastases |
| Intervention | Surgical resection combined with radiotherapy |
| Control | Monotherapy (surgical resection only, or radio therapy only) |
| Outcomes | Overall survival, locoregional control, disease-free survival, morbidity (e.g. toxicity, side effects), quality of life |
| Other selection criteria | Study design: systematic reviews and randomized controlled trials |

Relevant outcome measures

The guideline panel considered overall survival, breast-cancer specific survival, local recurrence, regional recurrence, distant metastases, and breast cancer events as a critical outcome measure for decision making; and local control, toxicity, side effects, quality of life, and patient-reported outcomes as an important outcome measure for decision making.

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

The guideline panel defined an absolute difference of 5% for all outcomes as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until November 14th, 2024. The detailed search strategy is depicted under the tab Methods. A single search strategy was used for four modules addressing local treatment of locoregional recurrences. The systematic literature search resulted in 992 hits. Studies were selected based on the following criteria: (1) breast cancer recurrence; (2) radiotherapy OR local excision OR breast-conserving surgery OR neoadjuvant therapy OR salvage mastectomy. Titles and abstracts were screened using the ASReview software. The settings *TF-IDF* and *Naïve bayes* were used. Walstra (2019) was used as prior knowledge for inclusion. The first 10% of hits were screened by the working group and the guideline methodologist. The remaining articles were subsequently screened by the guideline methodologist, using the following stopping rule: stop after 10% of the total set subsequent exclusions.
Based on title and abstract, one article was initially selected. After screening the full-text articles, one study was excluded, and no studies were included (see the table with reasons for exclusion under the tab Methods).

**Summary of literature**

Description of studies

No studies were included in the analysis of the literature.

Results

No studies were included in the analysis of the literature.

Summary of Findings

No studies were included in the analysis of the literature.

**Kennisvragen**

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:
Kun je de MARI procedure toepassen bij een regionaal recidief van de axilla?
Leidt toepassing van het MARI-principe bij patiënten met een geïsoleerd axillair recidief van borstkanker tot vergelijkbare of betere oncologische uitkomsten, met minder morbiditeit, vergeleken met standaard okselklierdissectie?

Toelichting:
PICO-vraag:
Bij patiënten met een geïsoleerd regionaal (axillair) recidief van borstkanker:
P (Population): vrouwen met een geïsoleerd regionaal (axillair) recidief van borstkanker zonder afstandsmetastasen, eerder behandeld met curatieve intentie;
I (Intervention): behandeling volgens het MARI-principe (verwijdering van de eerder gemarkeerde okselklier na systemische therapie);
C (Comparator): standaardbehandeling met okselklierdissectie
O (Outcomes): regionale controle, ziektevrije overleving, totale overleving, complicaties (zoals lymfoedeem en zenuwschade), kwaliteit van leven en patiëntgerapporteerde uitkomsten

De huidige evidentie over de behandeling van axillaire recidieven is beperkt en grotendeels gebaseerd op retrospectieve studies. Het is onbekend of de MARI-procedure, die bij primaire borstkanker wordt toegepast om okselchirurgie te beperken na neo-adjuvante therapie, ook veilig en effectief kan worden gebruikt bij regionale recidieven.

Een prospectieve multicenter cohortstudie of een fase II non-inferiority-trial wordt aanbevolen om deze vraag te beantwoorden. Hierbij kunnen naast oncologische uitkomsten ook complicaties, lymfoedeem, kwaliteit van leven en patiëntvoorkeuren worden geëvalueerd.

De resultaten van dergelijk onderzoek kunnen leiden tot vermindering van chirurgische morbiditeit en een meer gepersonaliseerde regionale behandeling bij patiënten met een regionaal recidief.

**Implementeren-tabel**
De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

***Implementatietabel***

| ***Vraag*** | ***Antwoord:*** *Kruis aan en licht toe/ beschrijf* | | ***Toelichting keuze:*** |
|---|---|---|---|
| **I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?** | **x** | **Ongewenste praktijkvariatie** | Er bestaan verschillen tussen ziekenhuizen in de benadering van patiënten met een regionaal recidief, met name in de keuze en volgorde van chirurgie, radiotherapie en systemische therapie. De werkgroep wil met deze module meer uniformiteit brengen in |

| | | | |
|---|---|---|---|
| | | | besluitvorming en timing van lokale behandeling. |
| | | **Nieuwe evidentie** | |
| | | **Anders** | |
| **I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?** | | **< 1000** | |
| | **X** | **< 5000** | |
| | | **5000-40.000** | |
| | | **> 40.000** | |
| **I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?** | **x** | **Ja** | De aanbeveling maakt onderdeel uit van een bredere set interventies voor de behandeling van regionaal recidief bij borstkanker. Deze module beschrijft de lokale behandeling, terwijl de systemische behandeling wordt behandeld in module 9.2.4. |
| | | **Nee** | |
| **I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:** | | **Belemmerende factoren** | **Bevorderende factoren/ kansen** |
| **Richtlijn/ klinisch traject (innovatie)** | | Beperkte evidence; conditionele aanbeveling vereist klinische afweging. | Bestaande praktijk is grotendeels in lijn met de aanbeveling; versterkt uniformiteit van beleid. |
| **Zorgverleners (artsen en verpleegkundigen)** | | Variatie in ervaring met re-irradiatie of salvagechirurgie; capaciteit voor multidisciplinair overleg. | Bestaande multidisciplinaire oncologische structuren (MDO's) ondersteunen gezamenlijke besluitvorming. |
| **Patiënt/ cliënt (naasten)** | | | |
| **Sociale context** | | | |
| **Organisatorische context** | | Herbestraling en hyperthermie niet in elk centrum beschikbaar; verwijzing nodig | Concentratie van complexe zorg in gespecialiseerde centra vergroot kwaliteit en veiligheid. |

| **Financiële en juridische context** | | | |
|---|---|---|---|
| **I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)**<br><br>**B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.* | | **A** | **B** |
| | | Patiënt/ cliënt (naaste) | |
| | **x** | Professional | Kennis nemen richtlijn |
| | **x** | Beroepsvereniging, nl | Richtlijn verspreiden, onder aandacht. |
| | | Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ) | |
| | | Zorgverzekeraars/ NZa | |
| | | Zorginstituut [duiding nodig] | |
| | | Anders | |
| **I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?** | **x** | < 1 jaar | |
| | | binnen 2-3 jaar | |
| **I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling?**<br>*De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.* | | Ja | |
| | **x** | Nee | De reguliere implementatieroutes (publicatie via Richtlijnendatabase, verspreiding via beroepsverenigingen) zijn voldoende. Extra maatregelen zijn niet nodig. |
| **I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst.**<br>*Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.* | | Ja * | |
| | **x** | Nee | De aanbeveling betreft bestaande zorgpraktijk. Geen extra implementatie-impuls nodig; focus ligt op bestendiging van uniform beleid. |

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

**Risk of Bias tables**

-

## 5 Table of excluded studies

| Reference | Reason for exclusion |
|---|---|
| Wadasadawala T, Vadgaonkar R, Bajpai J. Management of Isolated Locoregional Recurrences in Breast Cancer: A Review of Local and Systemic Modalities. Clin Breast Cancer. 2017 Nov;17(7):493-502. doi: 10.1016/j.clbc.2017.03.008. Epub 2017 Mar 21. PMID: 28396099. | Wrong study design |

**Literature search strategy**

10 ***Zoekverantwoording***

***Algemene informatie***

| | |
|---|---|
| Cluster/richtlijn:NIV Borstkanker | |
| Uitgangsvraag/modules: Recidief | |
| Database(s): Embase.com, Ovid/Medline | Datum: 13-11-2024 |
| Periode: vanaf 2010 | Talen: geen restrictie |
| Literatuurspecialist: Ingeborg van Dusseldorp | Rayyan review: https://rayyan.ai/reviews/1158129 |
| 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:**<br>Bij deze vraag horen 3 PICO's:<br>Patiënten met een lokaal recidief, I = lokale excisie of radiotherapie<br>Patiënten met een lokaal recidief, I = borstsparende operatie<br>Patiënten met een regionaal recidief, I = neo-adjuvant, chirurgie of radiotherapie<br><br>Uit de sleutelartikelen blijkt dat er veel overlap is. Met de adviseur wordt afgesproken dat een overkoepelende zoekstrategie zal worden uitgezet, waarbij is gezocht met de concepten:<br><br>Breastcancer recurrence AND (radiotherapy OR local excision OR breast-conserving surgery OR neoadjuvant therapy or salvage mastectomy)<br><br>Omdat er veel literatuur wordt gevonden, is besloten om de selectie met ASReview te doen. Vanwege de aantallen wordt gestart met alleen de SRs (afgestemd met Tim), in de hoop dat we een bruikbare SR vinden van waaruit we een aanvulling kunnen doen naar primaire studies.<br>Op een later moment kunnen de clinical trials worden toegevoegd als het nodig mocht zijn. Deze zijn opgeslagen in OneDrive.<br><br>Als prior knowledge kan de SR worden toegevoegd:<br>Repeat breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review<br>Walstra C.J.E.F., Schipper R.-J., Poodt I.G.M., van Riet Y.E., Voogd A.C., van der Sangen M.J.C., Nieuwenhuijzen G.A.P.<br>*European Journal of Surgical Oncology* 2019 45:8 (1317-1327) |
| Te gebruiken voor richtlijntekst:<br>In de databases Embase.com en Ovid/Medline is op 14-11-2024 systematisch gezocht naar systematische reviews, over de behandeling van teruggekeerde borstkanker. De literatuurzoekactie leverde 992 unieke treffers op. |

***Zoekopbrengst***

| | **EMBASE** | **OVID/MEDLINE** | **Ontdubbeld** |
|---|---|---|---|
| SR | 917 | 620 | 992 |
| RCT | 2249 | 1219 | 2381 |
| Observationele studies | | | |
| **Totaal** | | | **3373** |

5

***Zoekstrategie***

**Embase.com**

| No. | Query | Results |
|---|---|---|

| | | |
|---|---|---|
| #1 | ('breast cancer'/exp OR ((breast NEAR/3 (cancer* OR neoplasm* OR malignan* OR onco* OR carcinom* OR carcinogen*)):ti,ab,kw)) AND ('recurrent disease'/exp OR 'salvage therapy'/exp OR recurren*:ti,ab,kw OR relaps*:ti,ab,kw OR (('second conservative' NEAR/2 (therap* OR treatment*)):ti,ab,kw) OR ((salvage NEAR/3 (ablatio OR therap* OR treatment* OR mastectom*)):ti,ab,kw)) | 80595 |
| #2 | 'breast cancer recurrence'/exp OR (('breast cancer' NEAR/5 (recurrenc* OR relaps*)):ti,ab,kw) OR 'ipsilateral breast tumor recurrence'/exp OR (('ipsilateral* breast' NEAR/3 (event* OR recurren* OR relaps*)):ti,ab,kw) | 15562 |
| #3 | ('breast-conserving surgery'/exp OR 'mastectomy'/exp OR mastectom*:ti,ab,kw OR lumpectom*:ti,ab,kw OR ((breast NEAR/3 (amputat* OR exision* OR extirpat* OR removal* OR resect*)):ti,ab,kw) OR ((breast NEAR/3 (conserv* OR sparing)):ti,ab,kw)) AND ('recurrent disease'/exp OR recurren*:ti,ab,kw OR relaps*:ti,ab,kw) | 22344 |
| #4 | #1 OR #2 OR #3 | 82049 |
| #5 | 'radiotherapy'/exp 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 | 1327880 |
| #6 | 'local excision'/exp OR 'repeat procedure'/exp OR ((local NEAR/2 (resection OR excision)):ti,ab,kw) OR (((repeat* OR redo OR second OR previous) NEAR/3 (breast OR mamma*) NEAR/3 (conserv* OR sparing)):ti,ab,kw) OR 'axillary lymph node dissection'/exp OR ((axillar* NEAR/3 (dissect* OR excision* OR extirpat* OR lymphadenectom*)):ti,ab,kw) OR 'repeat* sentinel lymph node procedure':ti,ab,kw | 48020 |
| #7 | 'neoadjuvant therapy'/exp OR ((('neo adjuvant*' OR neoadjuvant*) NEAR/4 (chemo* OR therap* OR hormon* OR immuno* OR treatment*)):ti,ab,kw) | 111541 |
| #8 | #5 OR #6 OR #7 | 1389643 |
| #9 | #4 AND #8 | 28236 |
| #10 | #9 AND [2010-2025]/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) | 11829 |

| | | |
|---|---|---|
| #11 | '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 | 1061867 |
| #12 | '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 | 4140746 |
| #13 | #10 AND #11 | 917 |
| #14 | #10 AND #12 NOT #13 | 2249 |
| #15 | #13 OR #14 | 3166 |
| #16 | 'multidisciplinary management of locoregional recurrent breast cancer':ti | 1 |
| #17 | 'repeat breast-conserving therapy for ipsilateral breast cancer recurrence: a systematic review':ti | 1 |
| #18 | 're-irradiation and hyperthermia in breast cancer':ti AND oldenborg | 1 |
| #19 | 'second conservative treatment for local recurrence breast cancer: a gec-estro oncological outcome and prognostic factor analysis':ti | 1 |
| #20 | #16 OR #17 OR #18 OR #19 | 4 |
| #21 | #15 AND #20 | 1 |
| #22 | #20 NOT #21 | 1 |

**Ovid/Medline**

5

| # | Searches | Results |
|---|---|---|

| | | |
|---|---|---|
| 1 | (exp Breast Neoplasms/ or (breast adj3 (cancer* or neoplasm* or malignan* or onco* or carcinom* or carcinogen*)).ti,ab,kf.) and (Neoplasm Recurrence, Local/ or exp Recurrence/ or recurren*.ti,ab,kf. or relaps*.ti,ab,kf. or (salvage adj3 (ablatio or therap* or treatment* or mastectom*)).ti,ab,kf.) | 49811 |
| 2 | ((breast cancer adj5 (recurrenc* or relaps*)) or (ipsilateral* breast adj3 (event* or recurren* or relaps*))).ti,ab,kf. | 8961 |
| 3 | (exp Mastectomy/ or mastectom*.ti,ab,kf. or lumpectom*.ti,ab,kf. or (breast adj3 (amputat* or exision* or extirpat* or removal* or resect*)).ti,ab,kf. or ((breast or mamma*) adj3 (conserv* or sparing)).ti,ab,kf.) and (exp Recurrence/ or recurren*.ti,ab,kf. or relaps*.ti,ab,kf.) | 12563 |
| 4 | 1 or 2 or 3 | 50357 |
| 5 | 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. | 870695 |
| 6 | Reoperation/ or exp Lymph Node Excision/ or (local adj2 (resection or excision)).ti,ab,kf. or ((repeat* or redo or second or previous) adj3 (sentinel lymph node procedure or breast or mamma*) adj3 (conserv* or sparing)).ti,ab,kf. or (axillar* adj3 (dissect* or excision* or extirpat* or lymphadenectom*)).ti,ab,kf. | 168619 |
| 7 | Neoadjuvant Therapy/ or ((neo adjuvant or neoadjuvant) adj4 (therap* or chemo* or immuno* or hormon* or treatment*)).ti,ab,kf. | 59198 |
| 8 | 5 or 6 or 7 | 1059732 |
| 9 | 4 and 8 | 16162 |
| 10 | limit 9 to yr="2010 -Current" | 9482 |
| 11 | 10 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) | 9241 |

| | | |
|---|---|---|
| 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. | 787496 |
| 13 | 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. | 1769363 |
| 14 | 11 and 12 | 620 |
| 15 | 11 and 13 | 1219 |
| 16 | 14 or 15 | 1571 |

# Bijlagen bij module 6.1. Autologe vettransplantatie

**Kennisvragen**

Tijdens de ontwikkeling van deze module is systematisch naar onderzoeken gezocht die de zoekvraag kunnen beantwoorden. Door gebruik te maken van een systematische literatuuranalyse met beoordeling van de bewijskracht is duidelijk geworden dat er binnen deze module nog kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

*Kennisvraag -1*:
Wat zijn de (lange termijn)effecten van autologe vettransplantatie op oncologische veiligheid, kwaliteit van leven, complicaties en esthetisch resultaat bij vrouwen met borstkanker na ablatio, vergeleken met andere reconstructieve opties?

*Toelichting-1*:
Er is behoefte aan goed opgezette prospectieve cohortstudies die AFT vergelijken met implantaat- of autologe lapreconstructies. Met name inzicht in oncologische veiligheid op langere termijn en de impact van meerdere behandelsessies op kwaliteit van leven en kosteneffectiviteit zijn nodig om patiënten goed te kunnen informeren en begeleiden in het keuzeproces.

**Implementeren-tabel**

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De (cluster)werkgroep vult de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

***Implementatietabel***

| ***Vraag*** | ***Antwoord:*** *Kruis aan en licht toe/ beschrijf* | | ***Toelichting keuze:*** |
|---|---|---|---|
| **I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?** | **x** | **Ongewenste praktijkvariatie** | verschillen tussen centra in het aanbieden van AFT na borstkanker, met name aanbieden / bespreken van deze vorm van reconstructie |
| | **x** | **Nieuwe evidentie** | BREAST trial |
| | | **Anders** | |
| **I2. Maak een inschatting over hoeveel patiënten per jaar het ongeveer gaat waar de aanbeveling betrekking op heeft?** | **x** | **< 1000** | |
| | | **< 5000** | |
| | | **5000-40.000** | |
| | | **> 40.000** | |
| | | **Ja** | |

| | | | |
|---|---|---|---|
| **I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?** | **x** | **Nee** | |
| **I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:** | | **Belemmerende factoren** | **Bevorderende factoren/ kansen** |
| **Richtlijn/ klinisch traject (innovatie)** | **x** | Onzekerheid over oncologische veiligheid op lange termijn. | AFT is erkend als reconstructieve techniek, wordt al in meerdere centra toegepast, positieve patiëntgerapporteerde uitkomsten. |
| **Zorgverleners (artsen en verpleegkundigen)** | **x** | Leercurve voor plastisch chirurgen, beperkte ervaring in sommige centra, personeelscapaciteit. | Techniek relatief eenvoudig, bestaande infrastructuur aanwezig, motivatie hoog bij specialisten. |
| **Patiënt/ cliënt (naasten)** | **x** | Meerdere behandelsessies nodig, ongemakken bij gebruik EveBra, mogelijk hogere belasting. | Natuurlijker esthetisch resultaat, hogere tevredenheid en betere kwaliteit van leven dan na IBR. |
| **Sociale context** | | | |
| **Organisatorische context** | | Capaciteit en kennis op breed vlak | Er ontbreekt kennis over de methode bij mammacare en oncologisch chirurgen |
| **Financiële en juridische context** | | | |
| **I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)** | | **A** | **B** |
| | **x** | Patiënt/ cliënt (naaste) | Goede voorlichting, gedeelde besluitvorming, realistische verwachtingsmanagement |

| | | | |
|---|---|---|---|
| **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.* | | | (meerdere sessies, mogelijk kleiner volume). |
| | **x** | Professional | Scholing en training in AFT-techniek, scholing en training van aanpalende specialismes, integratie in MDO, duidelijke communicatie met patiënten over opties en belasting. |
| | **x** | Beroepsvereniging, nl NVPC | Bekendheid met de richtlijn, scholingsmodules en nascholing aanbieden. |
| | | Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ) | |
| | | Zorgverzekeraars/ NZa | |
| | | Zorginstituut [duiding nodig] | |
| | | Anders | |
| **I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?** | | < 1 jaar | |
| | **x** | binnen 2-3 jaar | Essentieel om kennis, scholing en infrastructuur breed in te bedden. |
| **I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling?** *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.* | | Ja | |
| | **x** | Nee | De aanbeveling gaat om het aanbieden van AFT als optie en om gedeelde besluitvorming. De techniek zelf is al beschikbaar in veel centra. Implementatie kan goed via reguliere kanalen verlopen (richtlijnpublicatie, nascholing, patiënteninformatie). Wel kan het behulpzaam zijn om ondersteunend materiaal zoals keuzehulpen of patiëntfolders te ontwikkelen, en om |

| | | | |
|---|---|---|---|
| | | | scholing in gespreksvoering te stimuleren alsook bredere scholing voor mammacare en oncologische chirurgen aan te bieden. |
| **I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst.** *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.* | | Ja * | |
| | **x** | Nee | |

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

**Background**

Autologous fat transfer is a relatively new breast reconstruction technique compared to other reconstruction methods that use implants or autologous flaps. The aim of this module is to create clarity in the efficacy and safety of autologous fat transfer compared to other reconstruction methods.

**Search and select**

A systematic review of the literature was performed to answer the following question(s):

What are the effects of autologous fat transfer compared to implant-based or autologous flap reconstruction on volume, oncological safety, (locoregional) oncological events, complications, patient satisfaction, disease-specific quality of life, and number of treatment sessions in women with breast cancer who undergo breast reconstruction after mastectomy or breast conserving surgery?

**Table 1. PICO**

| | |
|---|---|
| Patients | Patients who underwent breast conserving therapy or breast reconstruction after mastectomy for breast cancer |
| Intervention | Breast reconstruction after mastectomy using autologous fat transfer |
| Control | No reconstruction (only mastectomy), implant-based breast reconstruction after mastectomy or autologous flap reconstruction after mastectomy |

| | |
|---|---|
| Outcomes | Breast volume, oncological safety, (locoregional) oncological events, adverse events, patient satisfaction, disease-specific quality of life, number of treatment sessions |
| Other selection criteria | Study design: systematic reviews.<br>Minimal follow-up: 1 year |

Relevant outcome measures

The guideline panel considered breast volume, oncological safety, (locoregional) oncological events, and complications as a **critical** outcome measure for decision making; and patient satisfaction, disease-specific quality of life, and number of treatment as an **important** outcome measure for decision making.

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

The guideline panel defined the following as a minimal clinically (patient) important difference:

- Breast volume RR ≤0.85 or ≥1.15 (dichotomous); 0.5 SD (continuous).
- Oncological safety RR ≤0.95 or ≥1.05 (dichotomous); 0.5 SD (continuous); hazard ratio ≤ 1.3 (for non-inferiority).
- (locoregional) oncological events: a hazard ratio ≤ 1.3 (for non-inferiority)
- Complications RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous).
- Patient satisfaction: minimum three out of four domains with a 4 points difference on the BREAST-Q
- Disease specific quality of life: 4 points on the BREAST-Q or a difference of a similar magnitude on other validated quality of life instruments
- Number of treatment sessions RR ≤0.67 or ≥1.50 (dichotomous); 0.5 SD (continuous).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 1-1-2013 to 21-1-2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from 2 primary search concepts: (1) breast reconstruction AND (2) autologous fat transplantation. The detailed search strategy is listed under the tab 'Literature search strategy'. The systematic literature search resulted in 904 hits. Studies were selected based on the following criteria:

- Systematic reviews (searched in at least two databases, detailed search strategy with search date, in- and exclusion criteria, exclusion table, risk of bias assessment and results of individual studies available) or randomized clinical trials (RCTs);
- Full-text English language publication; and
- Studies according to the PICO.

Initially, 28 studies were selected based on title and abstract screening. After reading the full text, 24 studies were excluded (see the exclusion table under the tab 'Evidence tabellen') and four studies were included.

**Summary of literature**

Description of studies

Four studies were included in the analysis of the literature, including one randomized controlled trial (Piatkowski 2023) and three systematic reviews of observational studies (Tian 2022, Tukiama 2022, Goncalves 2022). Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

**Randomized controlled trial**

Piatkowski (2023) performed a multicenter randomized controlled trial (BREAST trial) comparing autologous fat transfer (AFT) to implant-based reconstruction (IBR) in women who underwent total breast reconstruction after mastectomy. The study was conducted in 7 hospitals across the Netherlands from November 2nd, 2015 to October 31st, 2021. A total of 193 women (≥ 18 years) with a history of or indication for mastectomy were randomized (1:1, stratified by center) to receive either AFT or IBR. Key exclusion criteria included recent smoking (<4 weeks), substance misuse, and prior radiotherapy to the breast. The primary outcome was quality of life at 12 months, assessed using the BREAST-Q v1.0. Secondary outcomes included breast volume (via 3D imaging), complications, and oncological safety. AFT involved serial fat grafting supported by an external expansion device (EveBra). Patients in the AFT group underwent more procedures (mean 4.2) over a longer period (mean 13.4 months) compared to IBR (mean 1.7 procedures; 5.1 months).

**Systematic reviews of observational studies**

All the SRs summarized below compared AFT to no treatment. With this comparison there is more risk of confounding by indication: patients who undergo breast reconstruction tend to have more favorable baseline prognostic factors (e.g., earlier cancer stage, better overall health) than those who do not, potentially biasing oncological outcomes in favor of AFT. This bias limits the interpretability of non-randomized comparisons between AFT and no reconstruction.

To mitigate this, data from the randomized controlled trial (RCT) by Piatkowski (2023) were used where applicable, as it provides a direct comparison of AFT versus implant-based reconstruction, thereby avoiding confounding by indication. For outcomes where the RCT reported results—specifically quality of life, breast volume, complications, and number of procedures—only the RCT data were used in this guideline. For outcomes not reported by the RCT, such as oncological events (local recurrence, systemic recurrence, metastases, and survival), data from systematic reviews were included.

Tian (2022) performed a systematic review and meta-analysis to assess the oncological safety of autologous fat transfer (AFT) in breast reconstruction following breast cancer surgery. A systematic search was performed up to September 14, 2020. Studies were included if they described cohorts with patients diagnosed with breast cancer who underwent AFT after surgery (intervention) compared to those who did not (control). The main outcome measures were local recurrence rate (LR), regional recurrence rate (RRR), locoregional recurrence rate (LRR), distant metastases rate, systemic recurrence rate (SR) and total death rate. Exclusion was based on other types of experiments (animal, pharmacological, pharmacokinetic), inclusion of women with a history of breast cancer and surgical treatment, other study designs (reviews, meta-analyses, case reports, conference abstracts or letters), other interventions than AFT, and other outcomes not relevant to AFT. A total of 22 cohort studies were included, involving 9971 patients (3622 in the AFT group and 6349 controls).

The systematic review and meta-analysis of Tukiama (2022) examined whether autologous fat transfer (AFT) increases the risk of locoregional recurrence (LRR) in women previously treated for breast cancer (either breast-conserving surgery or mastectomy). The systematic search was up to July 20, 2021. Inclusion criteria were studies with breast cancer patients who underwent prior oncologic surgery (breast conserving/mastectomy) and received immediate or delayed AFT, compared to a control group without breast reconstruction with AFT. Selection of study designs was limited to RCTs and matched cohorts. Studies involving patients without breast cancer, ongoing trials, and non-comparative or lower-quality design (e.g. case reports) were excluded. Data from nine matched cohorts were included in the analysis. Across the included studies, data were pooled from a total of 2,953 patients—of whom 1171 underwent AFT and 1782 served as controls.

Goncalves (2022) performed a systematic review and meta-analysis to evaluate the oncological safety of AFT following breast cancer surgery. The systematic search was up to January 18, 2021. Included articles studied women with breast cancer who underwent surgery and subsequent reconstruction with AFT. These patients were compared to patients that underwent breast reconstruction without AFT. RCTs, cohort studies and case-control studies were allowed to be selected. Case-series, duplicate papers/data, and manuscripts without original data were excluded. A total of 15 studies involving 8,541 participants were included. Of these, 2932 had received AFT and 5609 served as controls. Study designs included 4 case-control studies and 11 cohort studies (both prospective and retrospective). The review assessed three main outcomes: overall survival (OS), disease-free survival (DFS), and local recurrence (LR).

**Table 2. Characteristics of included studies**

| Study | Participants | Comparison** | Follow-up | Outcome measures | Comments | Risk of bias (per outcome measure)* |
|---|---|---|---|---|---|---|
| **Individual studies** | | | | | | |
| Piatkowski (2023) | N at baseline<br>Intervention: 93<br>Control: 98<br><br>Age (mean, SD)<br>Intervention: 49.3 (10.3) years<br>Control: 49.1 (11.0) years<br><br>Only females were included | Intervention: breast reconstruction with AFT<br>Control: implant based reconstruction | 12 months | Quality of life, breast volume, adverse events (pre-specified list of with complications for the surgeons), number of treatment sessions | Drs. Piatkowski, Wederfoort, and Hommes received ZonMw grants; Dr. Hommes also received funding from the Dutch Ministry of Health. Dr. van der Hulst was an unpaid secretary for the Dutch | **Some concerns** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Breast Implant Registry. | |
| **Systematic reviews** | | | | | | |
| Goncalves (2022) | Cohort/case-control studies: 15<br><br>Total number of patients: 8541<br>Intervention: 2932<br>Control: 5609<br><br>Mean age was 48.1 years (41 – 53.6) for the ATF group and 49.1 years (41 – 56 years) for the control group. Age was described in 14 out of 15 studies.<br><br>All described participants were women as this was one of the inclusion criteria. | Intervention: breast reconstruction with AFT<br>Control: no reconstruction or no AFT | Seven studies reported a mean follow-up of 60 months, five studies had a follow-up range between 40 and 60 months. Three studies had a follow-up of less than 40 months. | Overall survival (OS), disease-free survival (DFS), and local recurrence rate (LR) | N/A | Adequate blinding and randomization lacked in almost all included studies. |
| Tian (2022) | Cohort studies: 20<br><br>Total number of patients: 9971<br>Intervention: 3622 | Intervention: breast reconstruction with AFT<br>Control: no AFT | No information was given on the follow-up times per individual studies in the review. | Local recurrence rate (LR), regional recurrence rate (RRR), locoregional recurrence rate (LRR), systemic | N/A | All included articles were considered high quality based on the Newcastle-Ottawa scale, although no additional details are |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Control: 6349<br><br>The mean age of participants is 49.8 years (22-76 years)<br><br>No information on sex was given. | | | recurrence rate (SR) | | available in the review. |
| Tukiama (2022) | Matched cohort studies: 9<br><br>Total number of patients: 4247<br>Intervention: 1590<br>Control: 2657<br><br>No information on age was given.<br><br>No information on sex of participants was given per individual study. | Intervention: breast reconstruction with AFT<br>Control: No AFT | There were two follow-up periods reported. The first period (between oncological surgery and first AFT session) was not reported by all individual studies, but ranged from 23 to 56 months. The second period (between burst session and last follow-up) was reported by all included studies and ranged from 31 to 67 months. | Locoregional recurrence rate (LRR) | N/A | All included articles were considered of good quality based on the levels of evidence according to the Oxford Centre for Evidence-Based Medicine. All studies had a negative score on the attrition bias domain. |

*For further details, see risk of bias table in the appendix
** If an RCT was available with comparison of AFT to IBR, results were reported for RCT only. Otherwise SRs of observational studies were used.

5 Results

The three included SRs compare AFT to no treatment and are at risk of confounding by indication: patients who undergo breast reconstruction tend to have more favorable baseline prognostic factors (e.g., earlier cancer stage, better overall health) than those who do not, potentially biasing oncological outcomes in favor of AFT.

To mitigate this, data from the randomized controlled trial (RCT) by Piatkowski (2023) were used where applicable, as it provides a direct comparison of AFT versus implant-based reconstruction, thereby avoiding confounding by indication. For outcomes where the RCT reported results—specifically quality of life, breast volume, complications, and number of procedures—only the RCT data were used in this guideline. For outcomes not reported by the RCT, such as oncological events (local recurrence, systemic recurrence, metastases, and survival), data from systematic reviews were included.

**1. Breast volume (critical)**

Piatkowski (2023) compared breast volume at 12 months in women who underwent reconstruction with autologous fat transfer (AFT; n = 64) or implant-based reconstruction (IBR; n = 68). The mean breast volume was 300.3 mL (SD 111.4) in the AFT group and 384.1 mL (SD 86.8) in the IBR group. The mean difference between groups was –83.8 mL (95% CI: –116.2 to –51.3).

**2. Complications – Adverse events (critical)**

Piatkowski (2023) reported serious adverse events (SAEs) at 12 months for both the AFT group (n=64) and the IBR group (n=68). A total of 26 serious SAEs were reported. Of these, 9 were related to oncological complications, 4 in the AFT group and 5 in the IBR group. In the IBR group, two cases of incomplete resection requiring re-excision, one new contralateral primary tumor, one case of metastasis, and one recurrence requiring reoperation were reported. In the AFT group, two new contralateral primary tumors, one case of metastasis, and one incomplete resection requiring re-excision were reported.

**3. Overall survival (critical)**

Four studies included in Goncalves (2022) reported on the outcome overall survival (OS) in patients who underwent breast reconstruction with autologous fat transfer (AFT) (Krastev, 2019; Seth, 2012; Silva-Vergara, 2017; Sorrentino, 2019). The study of Krastev (2019) was omitted by Goncalves due to concerns about potential publication bias. The pooled HR comparing AFT to no AFT was 0.80 (95% CI, 0.34 to 1.86) in favor of breast reconstruction with AFT. This pooled HR did not distinguish results of MST patients from results of BCS patients. Seth (2012) reported data from patients who underwent mastectomy, which showed an HR of 0.36 (95% CI, 0.11-1.19). There were no studies that only reported data from patients who underwent BCS. The other studies included both MST and BCS in their analysis. It was not possible to separate all the data in MST only and BCS only based on the systematic review of Goncalves (2022).These results are shown in a forest plot (Figure 1).

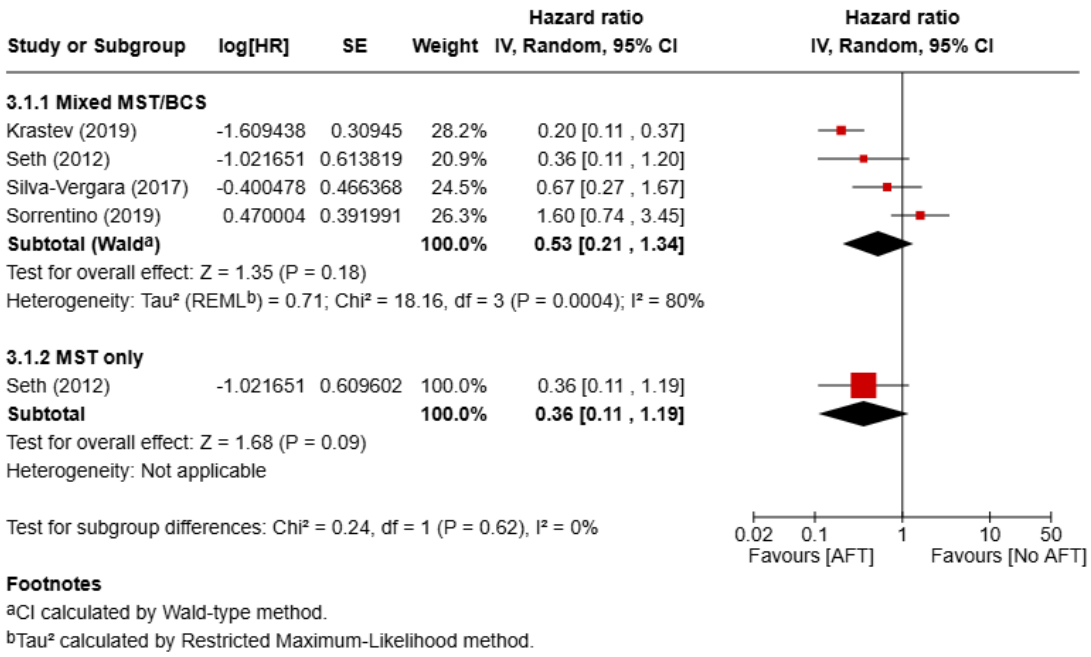


***Figure 1 Comparison of overall survival in patients with breast reconstruction with autologous fat transfer and no treatment or treatment without autologous fat transfer.*** *Z: p-value of the pooled effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval.*

5

### 4. Disease-free survival (critical)

Seven studies included in Goncalves (2022) reported on the outcome disease-free survival (DFS) in patients who underwent breast reconstruction with autologous fat transfer (AFT) (Cohen, 2017; Fertsch, 2017; Kronowitz, 2016; Masia, 2015; Silva-Vergara, 2017; Sorrentino, 2019; Stumpf, 2017). The pooled HR comparing AFT to no AFT was 0.90 (95% CI, 0.65 to 1.25) in favor of breast reconstruction with AFT. This pooled HR did not distinguish results of MST patients from results of BCS patients. Cohen (2017), Fertsch (2017) and Masia (2015) reported data from patients who underwent mastectomy, which showed a pooled HR of 0.76 (95% CI, 0.43-1.34). One study (Stumpf, 2017) reported data from patients who underwent BCS, with an HR of 0.58 (95% CI, 0.11-3.03). The other studies included both MST and BCS in their analysis. It was not possible to separate all the data in MST only and BCS only based on the systematic review of Goncalves (2022).These results are shown in a forest plot (Figure 2).

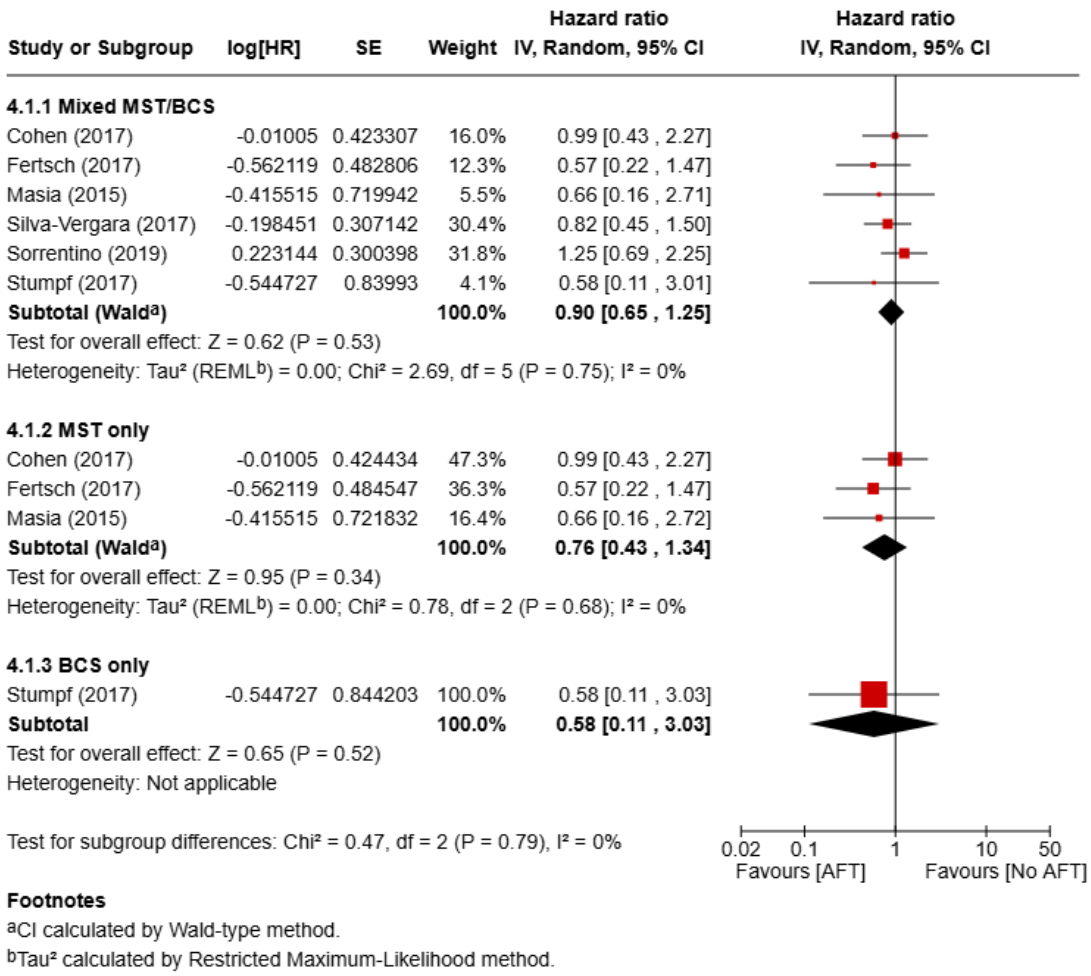


***Figure 2 Comparison of disease-free survival in patients with breast reconstruction with autologous fat transfer and no treatment or treatment without autologous fat transfer.*** *Z: p-value of the pooled effect; df: degrees of freedom; $I^2$: statistical heterogeneity; CI: confidence interval.*

### 5. Local recurrence (critical)

Eleven studies included in Tian (2022) reported on the outcome local recurrence (LR) in patients who underwent breast reconstruction with autologous fat transfer (AFT) (Cohen, 2017; Gale, 2015; Hanson, 2020; Masia, 2015; Petit, 2012; Petit, 2013; Petit, 2017; Seth, 2012; Silva-Vergara, 2017; Stumpf, 2017; Stumpf, 2020). The pooled RR comparing AFT to no AFT was 1.04 (95% CI, 0.76 to 1.43). This pooled HR did not distinguish results of mastectomy patients from results of BCS patients. There were five articles that reported data from patients who underwent mastectomy (Petit, 2013; Gale, 2015; Masia, 2015; Cohen, 2017; Silva-Vergara, 2017). This showed a pooled HR of 1.12 (95% CI, 0.60-2.10). Three studies (Petit, 2017; Stumpf, 2017; Stumpf, 2020) reported data from patients who underwent BCS, with an HR of 1.02 (95% CI, 0.64-1.62). The other studies included both mastectomy and BCS patients in their analysis. It was not possible to separate all the data in mastectomy only and BCS only based on the systematic review of Tian (2022). Results are presented in a forest plot (Figure 3).

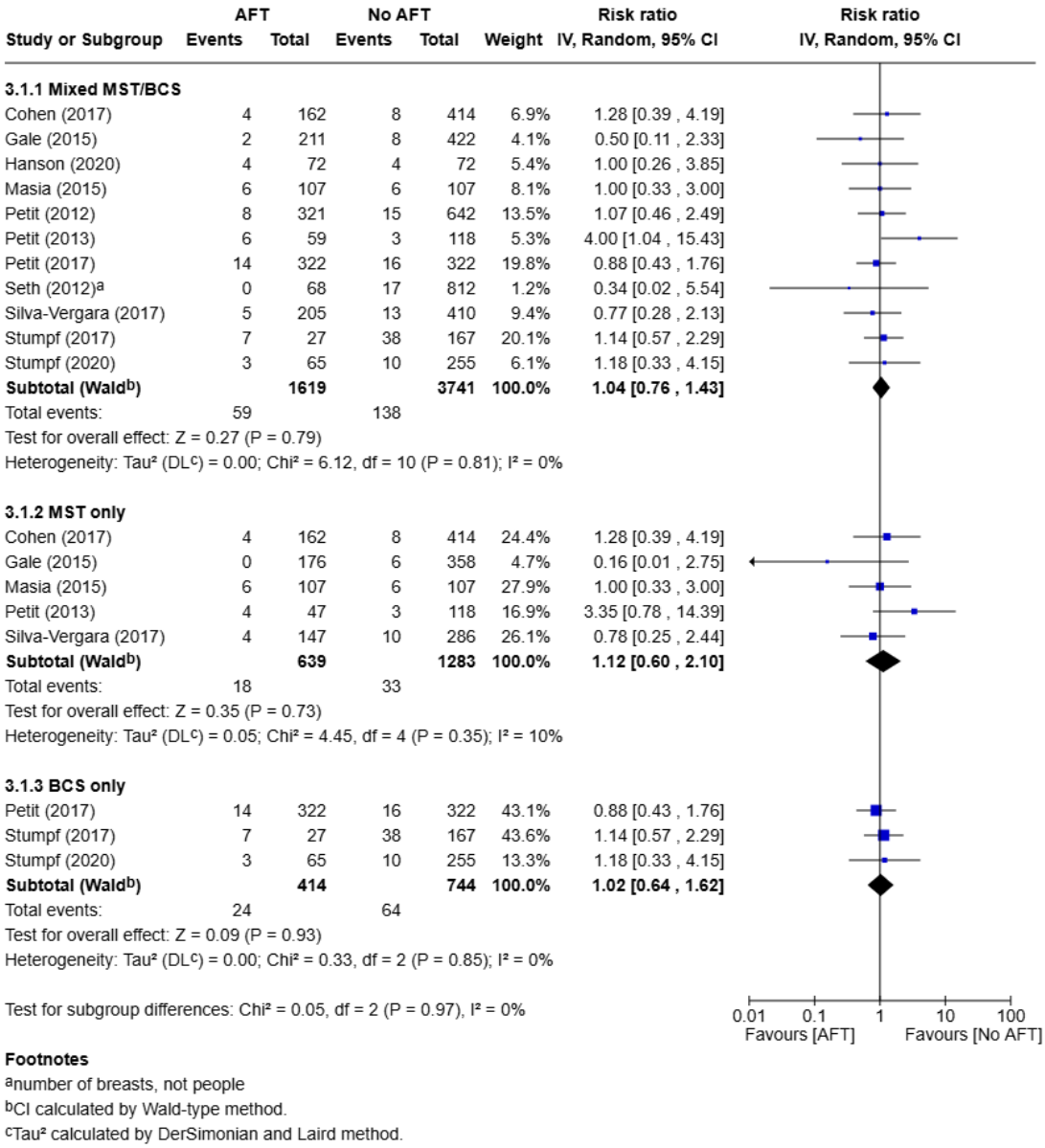


***Figure 3 Comparison of local recurrence in patients with breast reconstruction with autologous fat transfer and no treatment or treatment without autologous fat transfer.*** *Z: p-value of the pooled effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval.*

5

### 6. Locoregional recurrence (critical)

Fifteen studies included in Tian (2022) reported on the outcome locoregional recurrence (LRR) in patients who underwent breast reconstruction with autologous fat transfer (AFT) (Calabrese, 2018; Casarrubios, 2021; Fertsch, 2017; Gale, 2015; Kim, 2014; Krastev, 2019; 10 Kronowitz, 2016; Mestak, 2016; Petit, 2012; Petit, 2017; Pinell-White, 2015; Silva-Vergara, 2017; Sorrentino, 2019; Stumpf, 2020, Vyas, 2020). Tukiama, (2021) also reported on locoregional recurrence. The pooled relative risk (RR) comparing AFT to no AFT was 0.92 (95% CI, 0.72 to 1.18). This pooled HR did not distinguish results of mastectomy patients from results of BCS patients. There were six articles that reported data from patients who 15 underwent mastectomy (Gale, 2015; Fertsch, 2017; Silva-Vergara, 2017; Krastev, 2019; Casarrubios, 2021; Tukiama, 2021). This showed a pooled HR of 0.98 (95% CI, 0.53-1.80). Seven studies (Gale, 2015; Silva-Vergara, 2017; Petit, 2017; Stumpf, 2017; Krastev, 2019; Stumpf, 2020; Casarrubios, 2021; Tukiama, 2021) reported data from patients who underwent

BCS, with an HR of 0.83 (95% CI, 0.54-1.28). The other studies included both mastectomy and BCS patients in their analysis. It was not possible to separate all the data in mastectomy only and BCS only based on the systematic review of Tian (2022). Results are shown in a forest plot (Figure 4).

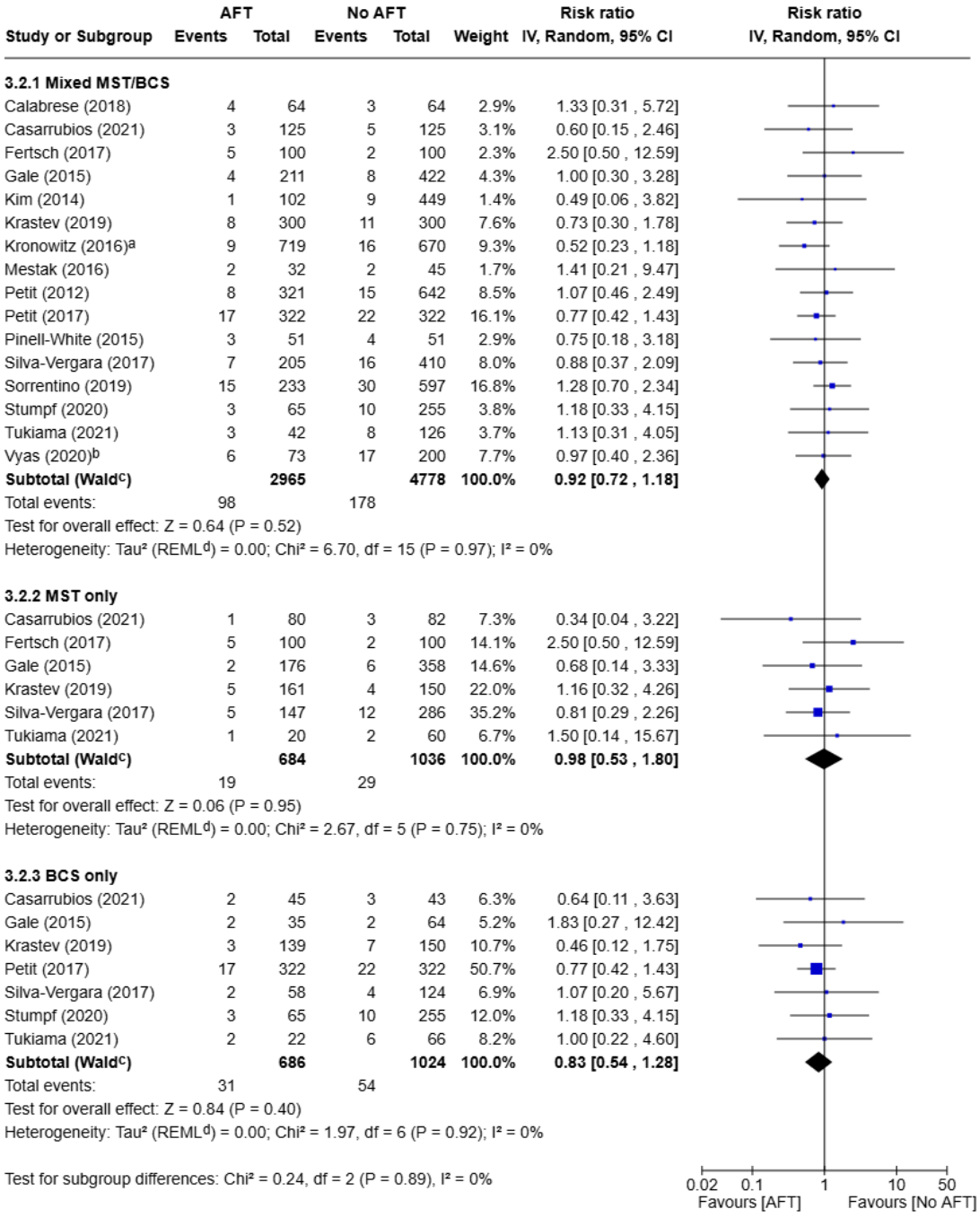


***Figure 4 Comparison of locoregional recurrence in patients with breast reconstruction with autologous fat transfer and no treatment or treatment without autologous fat transfer.*** *Z: p-value of the pooled effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval.*

## 7. Quality of life (important)

Piatkowski (2023) reported quality of life at 12 months postoperatively using the BREAST-Q questionnaire in patients who underwent breast reconstruction with autologous fat transfer (AFT; n = 64) or implant-based reconstruction (IBR; n = 68). The AFT group scored higher than the IBR group across all BREAST-Q domains. For three domains, the difference exceeded the predefined threshold for clinical relevance (≥4 points): satisfaction with breasts (AFT: 70.3 [SD 17.8] vs IBR: 60.4 [SD 17.2]; difference: 9.9), physical well-being (AFT: 79.9 [SD 14.7] vs IBR: 72.3 [SD 17.0]; difference: 7.6), and satisfaction with outcome (AFT: 73.9 [SD 22.4] vs IBR: 66.3 [SD 19.8]; difference: 7.6).

**8. Number of treatment sessions (important)**

Piatkowski (2023) reported a mean (SD) of 4.2 (1.2) procedures needed in the AFT group and 1.7 (0.5) for the IBR group. For the AFT group the number of sessions ranged from 2-7 sessions and for the IBR group, it ranged from 1-3 sessions.

Summary of Findings

Population: Patients who underwent breast reconstruction after mastectomy or breast conserving therapy for breast cancer
Intervention: Breast reconstruction after mastectomy using autologous fat transfer
Comparator: implant-based reconstruction/no treatment

| **Outcome**<br>**Timeframe** | **Study results and measurements** | **Absolute effect estimates**<br>No AFT/IBR AFT | **Certainty of the evidence**<br>**(Quality of evidence)** | **Summary** |
|---|---|---|---|---|
| Breast volume<br>(critical) | Higher better | 384.1 Mean<br>300.3 Mean<br>Difference: MD -83.8 lower<br>(CI 95% -116.2 lower - -51.3 lower) | **Low**<br>Due to serious risk of bias, Due to serious imprecision[1] | IBR may increase breast volume when compared with AFT in patients who underwent breast reconstruction (Piatkowski, 2023). |
| Complications – adverse events<br>(critical) | Reported by surgeons | 18 SAE were reported in the IBR group and 8 in the AFT group. Of these 5 in the IBR group and 4 in the AFT group were oncological. | **Low**<br>Due to serious risk of bias, Due to serious imprecision[2] | AFT may reduce serious adverse events when compared with IBR patients who underwent breast reconstruction (Piatkowski, 2023). |
| Overall survival<br>(critical) | Hazard ratio: 0.53<br>(CI 95% 0.21 - 1.34)<br>Based on data from 2918 participants in 4 studies | 33 per 1000<br>18 per 1000<br>Difference: 15 fewer per 1000<br>(CI 95% 26 fewer - 11 more) | **Very low**<br>Due to serious inconsistency, Due to serious imprecision[3] | The evidence is very uncertain about the effect of AFT on overall survival when compared with no AFT in patients who underwent breast reconstruction (Goncalves, 2022). |
| Disease-free survival<br>(critical) | Hazard ratio: 0.9<br>(CI 95% 0.65 - 1.25)<br>Based on data from 2629 participants in 6 studies | 85 per 1000<br>77 per 1000<br>Difference: 8 fewer per 1000<br>(CI 95% 29 fewer - 20 more) | **Very low**<br>Due to serious imprecision[4] | The evidence is very uncertain about the effect of AFT on disease-free survival when compared with no AFT in patients who underwent breast reconstruction (Goncalves, 2022). |
| Local recurrence<br>(critical) | Relative risk: 1.04<br>(CI 95% 0.76 - 1.43) | 36 per 1000<br>37 per 1000 | **Very low** | |

| | | | | |
|---|---|---|---|---|
| | Based on data from 5360 participants in 11 studies | Difference: 1 more per 1000 (CI 95% 9 fewer - 15 more) | Due to serious inconsistency, Due to serious imprecision[5] | The evidence is very uncertain about the effect of AFT on local recurrence when compared with no AFT in patients who underwent breast reconstruction (Tian, 2022; Tukiama, 2022). |
| Locoregional recurrence (critical) | Relative risk: 0.92 (CI 95% 0.72 - 1.18) Based on data from 7743 participants in 16 studies | 37 per 1000 — 34 per 1000<br>Difference: 3 fewer per 1000 (CI 95% 10 fewer - 7 more) | **Very low** Due to serious inconsistency, Due to serious imprecision[6] | The evidence is very uncertain about the effect of AFT on locoregional recurrence when compared with no AFT in patients who underwent breast reconstruction (Tian, 2022; Tukiama, 2022). |
| Quality of life *12 month* (important) | High better Based on data from 191 participants in 1 studies | BREAST-Q Satisfaction with breasts IBR: 60.4 (17.2) – AFT: 70.3 (17.8)<br>BREAST-Q Physical well-being (chest) IBR: 72.3 (17.0) – AFT: 79.9(14.7)<br>BREAST-Q Satisfaction with outcome IBR: 66.3 (19.8) – AFT: 73.9 (22.4) | **Very low** Due to serious risk of bias, Due to serious imprecision[7] | The evidence suggests AFT increases quality of life when compared with IBR in patients who underwent breast reconstruction (Piatkowski, 2023). |
| Number of treatment sessions (important) | Reported by surgeons | Piatkowski (2023) reported a mean (SD) of 4.2 (1.2) procedures needed in the AFT group and 1.7 (0.5) for the IBR group. For the AFT group the number of sessions ranged from 2-7 sessions and for the IBR group, this it ranged from 1-3 sessions. | **Very low** Due to serious risk of bias, Due to serious imprecision[8] | The evidence suggests AFT requires more treatment sessions compared with IBR in patients who underwent breast reconstruction (Piatkowski, 2023). |

1. **Risk of bias: serious.** Due to selective outcome reporting (no separate analysis for ITT and PP population) and lack of blinding due to nature of procedure; **Imprecision: serious.** Due to only one study reporting the outcome and small sample size;
2. **Risk of bias: serious.** Due to selective outcome reporting (no separate analysis for ITT and PP population) and lack of blinding due to nature of procedure; **Imprecision: serious.** Due to only one study reporting the outcome;
3. **Inconsistency: serious.** Due to variation of point estimates; **Imprecision: serious.** Confidence intervals are wide and cross one of the minimally clinical important difference thresholds;
4. **Imprecision: serious.** Confidence intervals are wide;
5. **Inconsistency: serious.** Due to variation of point estimates; **Imprecision: serious.** Confidence intervals are wide;
6. **Inconsistency: serious.** Due to variation of point estimates; **Imprecision: serious.** Confidence intervals are wide;
7. **Risk of bias: serious.** Due to selective outcome reporting (no separate analysis for ITT and PP population) and lack of blinding due to nature of procedure; **Imprecision: very serious.** Only point estimates available.
8. **Risk of bias: serious.** Due to selective outcome reporting (no separate analysis for ITT and PP population) and lack of blinding due to nature of procedure; **Imprecision: very serious.** Only point estimates available.

**Risk of Bias tables**

***Goncalves (2022)***

For further details about the risk of bias assessment, see:
https://doi.org/10.1186/s12885-022-09485-5

The authors used the Downs and Black instrument for adapted quality assessment. This tool assesses five domains: reporting, external validity, internal validity (bias), internal validity – confounding (selection bias), and power. Total score of 28, where 26-28 is scored as excellent and ≤14 as poor.

| *STUDIES Year of Publication* | *Fertsch 2019* | *Cohen 2017* | *Calabrese 2018* | *Cogliandro 2017* | *Khan 2017* | *Krastev 2019* | *Kronowitz 2015* | *Masia 2015* | *Mazur 2018* | *Petit 2012* | *Petit 2013* | *Seth 2012* | *Silva-Vergara 2017* | *Sorrentino 2019* | *Stumpf 2017* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Final score* | 18 | 20 | 20 | 19 | 16 | 23 | 22 | 22 | 12 | 22 | 20 | 23 | 23 | 19 | 15 |

***Tian (2022)***

The authors used the Newcastle-Ottawa scale for quality assessment of the included studies. This tool assesses literature based on three domains: selection, comparability, and outcome. Higher score means higher quality of the article, thus a lower risk of bias.

| Study | NOS scores |
|---|---|
| Petit (2012) | 6 |
| Seth (2012) | 6 |
| Petit (2013) | 7 |
| Kim (2014) | 5 |
| Gake (2015) | 7 |
| Laporta (2015) | 6 |
| Masia (2015) | 6 |
| Pinell-White (2015) | 5 |
| Nestak (2016) | 6 |
| Kronowitz (2016) | 7 |
| Cohen (2017) | 7 |
| Fertsch (2017) | 7 |
| Khan (2017) | 5 |
| Petit (2017) | 6 |
| Silva-Vergara (2017) | 7 |
| Stumpf (2017) | 6 |
| Calabrese (2018) | 7 |
| Krastev (2019) | 6 |
| Sorrentino (2019) | 6 |
| Hanson (2020) | 7 |
| Stumpf (2020) | 6 |
| Vyas (2020) | 6 |

***Tukiama (2022)***

The authors used the levels of evidence it the Oxford Centre for Evidence-Based Medicine to assess risk of bias. Nine studies were classified as good quality.

**Table 2**
Summary of characteristics of selected matched cohorts.

| Reference | Level of evidence[a] | Group | N | Histology | | Type of surgery | | Follow-up | | Locoregional recurrence (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | In situ (%) | Invasive (%) | BCS (%) | Mastectomy (%) | Period 1 (months) | Period 2 (months) | |
| Tukiama et al., 2021 [49] | 2b | AFG | 42 | 1 (2.4) | 41 (97.6) | 22 (52.4) | 20 (47.6) | 56 | 65 | 3 (7.1) |
| | | C | 126 | 3 (2.4) | 123 (97.6) | 66 (52.4) | 60 (47.6) | | 65 | 8 (6.3) |
| Casarrubios et al., 2021 [61] | 2b | AFG | 125 | 19 (15.2) | 106 (84.8) | 45 (36.0) | 80 (64.0) | 48 | 47 | 3 (2.4) |
| | | C | 125 | 10 (8.0) | 115 (92.0) | 43 (34.4) | 82 (65.6) | | 37 | 5 (4.0) |
| Stumpf et al., 2020 [47] | 2b | AFG | 65 | – | 65 (100) | 65 (100) | – | – | 64 | 3 (4.6) |
| | | C | 255 | – | 255 (100) | 255 (100) | – | | 67 | 10 (3.9) |
| Sorrentino et al., 2019 [48] | 2b | AFG | 233 | 26 (11.2) | 207 (88.8) | 54 (23.2) | 179 (76.8) | 23 | 51 | 15 (6.4) |
| | | C | 597 | 62 (10.4) | 535 (89.6) | 444 (74.4) | 153 (25.6) | | 41 | 30 (5.0) |
| Krastev et al., 2019 [42] | 2b | AFG | 300 | 39 (13.0) | 261 (87.0) | 139 (46.3) | 161 (53.7) | 52 | 60 | 8 (2.8) |
| | | C | 300 | 40 (13.3) | 260 (86.7) | 150 (50.0) | 150 (50.0) | | 53 | 11 (3.7) |
| Petit et al., 2017 [38] | 2b | AFG | 322 | – | 322 (100) | 322 (100) | – | … | 58 | 17 (5.3) |
| | | C | 322 | – | 322 (100) | 322 (100) | – | | 53 | 22 (6.8) |
| Silva-Vergara et al., 2017 [40] | 2b | AFG | 205 | 44 (21.5) | 161 (78.5) | 58 (28.3) | 147 (71.7) | 48 | 40 | 7 (3.4) |
| | | C | 410 | 75 (18.3) | 335 (81.7) | 124 (30.2) | 286 (69.8) | | 39 | 16 (3.9) |
| Fertsch et al., 2017 [41] | 2b | AFG | 100 | 9 (9.0) | 91 (91.0) | – | 100 (100) | 41 | 32 | 5 (5.0) |
| | | C | 100 | 9 (9.0) | 91 (91.0) | – | 100 (100) | | 31 | 2 (2.0) |
| Gale et al., 2015 [39] | 2b | AFG | 211 | 27 (12.8) | 184 (87.2) | 35 (16.6) | 176 (83.4) | 54 | 32 | 4 (1.9) |
| | | C | 422 | 54 (12.8) | 368 (87.2) | 64 (15.2) | 358 (84.8) | | 34 | 8 (1.9) |
| Total | … | AFG | 1603 | 165 (10.3) | 1438 (89.7) | 740 (46.2) | 863 (53.8) | … | … | … |
| | | C | 2657 | 253 (9.5) | 2404 (90.5) | 1468 (55.3) | 1189 (44.7) | | | |

Abbreviations: AFG, autologous fat grafting; C, control; BCS, breast-conserving surgery; (…) = non-informed, non-available data, or non-applicable; (–) = value equals to zero.
[a] Levels of evidence for studies assessing harm according to the Oxford Centre for Evidence-Based Medicine (2009).

### *Piatkowski (2023)*

| **Was the allocation sequence adequately generated?** | **Was the allocation adequately concealed?** | **Blinding: Was knowledge of the allocated interventions adequately prevented?**<br><br>**Were patients blinded?**<br><br>**Were healthcare providers blinded?**<br><br>**Were data collectors blinded?**<br><br>**Were outcome assessors blinded?**<br><br>**Were data analysts 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**<br>**If applicable/necessary, per outcome measure** |
|---|---|---|---|---|---|---|
| Probably yes;<br><br>Reason: Allocation mentioned, but not specified | No information | Probably no;<br><br>Reason: Due to the nature of the intervention, blinding was not possible (surgical intervention) | Probably yes;<br><br>Reason: Loss to follow-up was present, but equally distributed over the intervention and control group | Definitely no;<br><br>Reason: No separate analyses for ITT and PP population | Definitely yes;<br><br>Reason: No other problems noted | **Some concerns** |

## Table of excluded studies

| Reference | Reason for exclusion |
|---|---|
| Wederfoort JLM, Trommelen DAX, Al Tarah M, Hommes JE, van Kuijk SMJ, van der Hulst RRWJ, Piatkowski AA. Volumetric evaluation of autologous fat transfer for total breast reconstruction. J Plast Reconstr Aesthet Surg. 2024;99:317–28. doi:10.1016/j.bjps.2024.09.083. | Partially reports the same outcomes for the same population as Piatkowski (2023) (already included) and the additional outcomes are not relevant for the guideline module. |
| Lo Torto F, Patanè L, Abbaticchio D, Pagnotta A, Ribuffo D. Autologous Fat Grafting (AFG): A Systematic Review to Evaluate Oncological Safety in Breast Cancer Patients. J Clin Med. 2024 Jul 26;13(15):4369. doi: 10.3390/jcm13154369. PMID: 39124636; PMCID: PMC11313166. | Wrong design, limited description search strategy |
| Groen JW, Negenborn VL, Twisk DJWR, Rizopoulos D, Ket JCF, Smit JM, Mullender MG. Autologous fat grafting in onco-plastic breast reconstruction: A systematic review on oncological and radiological safety, complications, volume retention and patient/surgeon satisfaction. J Plast Reconstr Aesthet Surg. 2016 Jun;69(6):742-764. doi: 10.1016/j.bjps.2016.03.019. Epub 2016 Mar 29. PMID: 27085611. | Unclear comparison group |
| Tayeh S, Muktar S, Wazir U, Carmichael AR, Al-Fardan Z, Kasem A, Hamdi M, Mokbel K. Is Autologous Fat Grafting an Oncologically Safe Procedure following Breast Conserving Surgery for Breast Cancer? A Comprehensive Review. J Invest Surg. 2022 Feb;35(2):390-399. doi: 10.1080/08941939.2020.1852343. Epub 2020 Dec 11. PMID: 33302753. | Unclear comparison group |
| Al Qurashi AA, Shah Mardan QNM, Alzahrani IA, AlAlwan AQ, Bafail A, Alaa Adeen AM, Albahrani A, Aledwani BN, Halawani IR, AlBattal NZ, Mrad MA. Efficacy of Exclusive Fat Grafting for Breast Reconstruction: An Updated Systematic Review and Meta-analysis. Aesthetic Plast Surg. 2024 Dec;48(23):4979-4985. doi: 10.1007/s00266-024-03978-3. Epub 2024 May 21. PMID: 38772941. | Wrong design, nonsystematic search |
| Wang K, Yu Z, Rong X, Tang J, Dang J, Li H, Yang J, Peng H, Yi C. Meta-Analysis of the Oncological Safety of Autologous Fat Grafting After Breast Cancer on Basic Science and Clinical Studies. Aesthetic Plast Surg. 2023 Aug;47(4):1245-1257. doi: 10.1007/s00266-022-03217-7. Epub 2022 Dec 21. PMID: 36542092. | Wrong design |
| Vernice NA, Jung WF, Black GG, Demetres M, Otterburn DM. Streamlining the Fat: A Systematic Review of Active Closed Wash and Filtration in Autologous Fat Grafting After Breast Reconstruction. Aesthet Surg J. 2023 Nov 16;43(12):1481-1488. doi: 10.1093/asj/sjad153. PMID: 37210472; PMCID: PMC10653348. | Wrong design, wrong comparison |
| Samuels S, Adeboye T, Zafar AQ, Katsura C, Izard C, Shahrokhi N, Rahman S. Autologous Fat Grafting for Post-mastectomy Pain Syndrome: A Systematic Review and Meta-Analysis. Cureus. 2023 Nov 18;15(11):e49017. doi: 10.7759/cureus.49017. PMID: 38024082; PMCID: PMC10676735. | Wrong design, wrong population |

| | |
|---|---|
| Maheta B, Yesantharao PS, Thawanyarat K, Akhter MF, Rowley M, Nazerali RS. Timing of autologous fat grafting in implant-based breast reconstruction: Best practices based on systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2023 Nov;86:273-279. doi: 10.1016/j.bjps.2023.09.026. Epub 2023 Sep 14. PMID: 37797375. | Wrong population |
| Kuruvilla AS, Yan Y, Rathi S, Wang F, Weichman KE, Ricci JA. Oncologic Safety in Autologous Fat Grafting After Breast Conservation Therapy: A Systematic Review and Meta-analysis of the Literature. Ann Plast Surg. 2023 Jan 1;90(1):106-110. doi: 10.1097/SAP.0000000000003385. PMID: 36534109. | Wrong design |
| Wederfoort JLM, Hebels SA, Heuts EM, van der Hulst RRWJ, Piatkowski AA. Donor site complications and satisfaction in autologous fat grafting for breast reconstruction: A systematic review. J Plast Reconstr Aesthet Surg. 2022 Apr;75(4):1316-1327. doi: 10.1016/j.bjps.2022.01.029. Epub 2022 Jan 25. PMID: 35165073. | Wrong population |
| Sun J, Liang H, Lin D, Han B, Zhang T, Gao J. Oncological safety of reconstruction with autologous fat grafting in breast cancer patients: a systematic review and meta-analysis. Int J Clin Oncol. 2022 Sep;27(9):1379-1385. doi: 10.1007/s10147-022-02207-8. Epub 2022 Jul 5. PMID: 35790652. | Wrong design, better alternatives |
| Qin Z, Yu Z, Song B. Efficacy and Safety of External Volume Expansion (EVE) on Fat Grafting: A Systematic Review and Single-Arm Meta-Analysis. J Plast Reconstr Aesthet Surg. 2022 Mar;75(3):1073-1082. doi: 10.1016/j.bjps.2021.11.032. Epub 2021 Nov 16. PMID: 34930704. | Wrong population |
| Li M, Shi Y, Li Q, Guo X, Han X, Li F. Oncological Safety of Autologous Fat Grafting in Breast Reconstruction: A Meta-analysis Based on Matched Cohort Studies. Aesthetic Plast Surg. 2022 Jun;46(3):1189-1200. doi: 10.1007/s00266-021-02684-8. Epub 2022 Jan 3. PMID: 34981157. | Wrong design |
| Gentile P, Cervelli V. Systematic review: Oncological safety of reconstruction with fat grafting in breast cancer outcomes. J Plast Reconstr Aesthet Surg. 2022 Nov;75(11):4160-4168. doi: 10.1016/j.bjps.2022.08.026. Epub 2022 Aug 24. PMID: 36180337. | Wrong design |
| Alessandri Bonetti M, Carbonaro R, Borelli F, Amendola F, Cottone G, Mazzocconi L, Mastroiacovo A, Zingaretti N, Parodi PC, Vaienti L. Outcomes in Hybrid Breast Reconstruction: A Systematic Review. Medicina (Kaunas). 2022 Sep 6;58(9):1232. doi: 10.3390/medicina58091232. PMID: 36143908; PMCID: PMC9503593. | Wrong design |
| Wang K, Dai Y, Pan Y, Cheng P, Jin X. Local-regional recurrence risk after autologous fat grafting in breast cancer patients: A systematic review and meta-analysis. J | Wrong design |

| | |
|---|---|
| Surg Oncol. 2020 Mar;121(3):435-440. doi: 10.1002/jso.25829. Epub 2020 Jan 14. PMID: 31943238. | |
| Osswald R, Boss A, Lindenblatt N, Vorburger D, Dedes K. Does lipofilling after oncologic breast surgery increase the amount of suspicious imaging and required biopsies?-A systematic meta-analysis. Breast J. 2020 May;26(5):847-859. doi: 10.1111/tbj.13514. Epub 2019 Sep 11. PMID: 31512360. | Wrong design |
| Cohen S, Sekigami Y, Schwartz T, Losken A, Margenthaler J, Chatterjee A. Lipofilling after breast conserving surgery: a comprehensive literature review investigating its oncologic safety. Gland Surg. 2019 Oct;8(5):569-580. doi: 10.21037/gs.2019.09.09. PMID: 31741888; PMCID: PMC6842766. | Wrong design |
| Krastev TK, Schop SJ, Hommes J, Piatkowski AA, Heuts EM, van der Hulst RRWJ. Meta-analysis of the oncological safety of autologous fat transfer after breast cancer. Br J Surg. 2018 Aug;105(9):1082-1097. doi: 10.1002/bjs.10887. Epub 2018 Jun 5. PMID: 29873061; PMCID: PMC6055707. | Wrong design |
| Krastev TK, Alshaikh GAH, Hommes J, Piatkowski A, van der Hulst RRWJ. Efficacy of autologous fat transfer for the correction of contour deformities in the breast: A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2018 Oct;71(10):1392-1409. doi: 10.1016/j.bjps.2018.05.021. Epub 2018 Jun 8. PMID: 30061004. | Wrong population |
| Herly M, Ørholt M, Larsen A, Pipper CB, Bredgaard R, Gramkow CS, Katz AJ, Drzewiecki KT, Vester-Glowinski PV. Efficacy of breast reconstruction with fat grafting: A systematic review and meta-analysis. J Plast Reconstr Aesthet Surg. 2018 Dec;71(12):1740-1750. doi: 10.1016/j.bjps.2018.08.024. Epub 2018 Sep 4. PMID: 30245019. | Wrong design |
| Waked K, Colle J, Doornaert M, Cocquyt V, Blondeel P. Systematic review: The oncological safety of adipose fat transfer after breast cancer surgery. Breast. 2017 Feb;31:128-136. doi: 10.1016/j.breast.2016.11.001. Epub 2016 Nov 10. PMID: 27837706. | Wrong design |
| Wazir U, El Hage Chehade H, Headon H, Oteifa M, Kasem A, Mokbel K. Oncological Safety of Lipofilling in Patients with Breast Cancer: A Meta-analysis and Update on Clinical Practice. Anticancer Res. 2016 Sep;36(9):4521-8. doi: 10.21873/anticanres.10999. PMID: 27630291. | Wrong design |
| Spear SL, Coles CN, Leung BK, Gitlin M, Parekh M, Macarios D. The Safety, Effectiveness, and Efficiency of Autologous Fat Grafting in Breast Surgery. Plast Reconstr Surg Glob Open. 2016 Aug 8;4(8):e827. doi: 10.1097/GOX.0000000000000842. PMID: 27622095; PMCID: PMC5010318. | Wrong design |

**Literature search strategy**

| | |
|---|---|
| Cluster/richtlijn: NIV – borstkanker en borstreconstructie | |
| Uitgangsvraag/modules: Wat zijn de effecten van autologe vettransplantatie vergeleken met implantaat- en autologe reconstructie op volume, oncologische veiligheid, (locoregionale) oncologische events, complicaties, patiënttevredenheid, ziektespecifieke kwaliteit van leven en aantal behandelsessies bij vrouwen met borstkanker die een borstreconstructie ondergaan na mastectomie of borstsparende operatie? | |
| Database(s): Embase.com, Ovid/Medline | Datum: 21-1-2025 |
| Periode: vanaf 2013 | Talen: geen restrictie |
| Literatuurspecialist: Ingeborg van Dusseldorp | Rayyan review: https://new.rayyan.ai/reviews/1296466/ |
| 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:**<br>Voor deze vraag is gezocht met de concepten:<br>1. Autologe vet transplantatie<br>2. Borstreconstructie<br><br>Er worden meerdere data aangegeven om te limiteren. Er wordt van de oudste datum 2013. In de selectie kan datum als exclusiecriterium worden gehanteerd.<br>Alle sleutelartikelen, 11 stuks, worden gevonden. | |
| Te gebruiken voor richtlijntekst:<br>A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 1-1-2013 to 21-1-2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from 2 primary search concepts: (1) breast reconstruction AND (2) autologous fat transplantation. Duplicates were removed using EndNote software. After deduplication a total of 904 records were imported for title/abstract screening Initially, 28 studies were selected based on title and abstract screening. After reading the full text, 24 studies were excluded (see the exclusion table under the tab 'Evidence tabellen') and four studies were included. | |

***Zoekopbrengst***

| | **EMBASE** | **OVID/MEDLINE** | **Ontdubbeld** |
|---|---|---|---|
| SR | 122 | 109 | 134 |
| RCT | 133 | 106 | 170 |
| Observationele studies | 463 | 521 | 600 |
| **Totaal** | 718 | 736 | **904** |

****in Rayyan***

***Zoekstrategie***

**Embase.com**

| No. | Query | Results |
|---|---|---|

| | | |
|---|---|---|
| #1 | ('autograft'/de OR 'autotransplantation'/exp OR 'transplantation'/de) AND ('fat'/exp OR 'adipose tissue'/exp) OR ((lipo NEAR/2 (struct* OR transfer* OR transplant* OR model* OR fill*)):ti,ab,kw) OR lipotransplant*:ti,ab,kw OR lipostruct*:ti,ab,kw OR lipotransfer*:ti,ab,kw OR lipomodel*:ti,ab,kw OR lipofill*:ti,ab,kw OR ((fat* NEAR/3 (autolog* OR autotransplant* OR transplant* OR graft* OR transfer* OR inject* OR infiltrate*)):ti,ab,kw) OR 'reverse expan*':ti,ab,kw OR 'autologous fat'/de OR 'lipotransfer'/de OR 'lipomodelling'/de OR 'adipose tissue transplantation'/de OR 'autologous fat grafting'/de OR 'autologous fat transplantation'/de OR 'autologous fat transfer'/de OR 'autologous fat graft'/de OR 'autologous fat injection'/de | 18217 |
| #2 | 'breast tumor'/exp OR 'breast surgery'/exp OR mammaplast*:ti,ab,kw OR mammoplast*:ti,ab,kw OR mastoplast*:ti,ab,kw OR mastectom*:ti,ab,kw OR (((breast* OR mamma* OR ductal OR lobular) NEAR/3 (tumor* OR tumour* OR neoplas* OR carcino* OR cancer* OR malign*)):ti,ab,kw) OR (((breast* OR mamma*) NEAR/6 onco*):ti,ab,kw) OR mammacarcin*:ti,ab,kw OR phyllo?de*:ti,ab,kw OR (((breast* OR mamma*) NEAR/3 (surg* OR reconstruct*)):ti,ab,kw) OR lumpectom*:ti,ab,kw OR (((breast OR mamma*) NEAR/3 (conserv* OR spar* OR amputat* OR exision* OR excision* OR extirpat* OR removal* OR resect*)):ti,ab,kw) | 871952 |
| #3 | #1 AND #2 | 2204 |
| #4 | #3 AND [2013-2025]/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) | 956 |
| #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 | 1096528 |
| #6 | '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 |
| #7 | '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 | '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))) | 15725352 |
| #9 | #4 AND #5 | 122 |
| #10 | #4 AND #6 NOT #9 | 133 |
| #11 | #4 AND (#7 OR #8) NOT #9 NOT #10 | 463 |
| #12 | 'effect of total breast reconstruction with autologous fat transfer using an expansion device vs implants on quality of life among patients with breast cancer':ti | 1 |
| #13 | 'autologous fat grafting for post-mastectomy pain syndrome: a systematic review and meta-analysis':ti | 0 |
| #14 | 'the prognosis outcomes of autologous fat transfer for breast reconstruction after breast cancer surgery: a systematic review and meta-analysis of cohort studies':ti | 0 |
| #15 | 'the oncological safety of autologous fat grafting: a systematic review and meta-analysis':ti | 1 |
| #16 | 'oncologic safety of breast reconstruction with autologous fat grafting: a systematic review and meta-analysis':ti | 1 |
| #17 | 'donor site complications and satisfaction in autologous fat grafting for breast reconstruction: a systematic review':ti | 1 |
| #18 | ('08941939':is OR '15210553':is OR 'journal of investigative surgery'/jt) AND 2022 AND tayeh | 1 |

| | | |
|---|---|---|
| #19 | 'quality of life after autologous fat transfer additional to prosthetic breast reconstruction in women after breast surgery: a systematic review':ti | 1 |
| #20 | 'long-term follow-up of autologous fat transfer vs conventional breast reconstruction and association with cancer relapse in patients with breast cancer':ti | 1 |
| #21 | 'efficacy of autologous fat transfer for the correction of contour deformities in the breast: a systematic review and meta-analysis':ti AND 2018 NOT comment:ti | 1 |
| #22 | 'meta-analysis of the oncological safety of autologous fat transfer after breast cancer':ti | 2 |
| #23 | #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | 10 |
| #24 | #9 OR #10 OR #11 | 718 |

**Ovid/Medline**

| # | Searches | Results |
|---|---|---|
| 1 | ((Autografts/ or Transplantation, Autologous/ or Transplantation/) and (Fats/ or Adipose Tissue/)) or (lipo adj2 (struct* or transfer* or transplant* or model* or fill*)).ti,ab,kf. or lipotransplant*.ti,ab,kf. or lipostruct*.ti,ab,kf. or lipotransfer*.ti,ab,kf. or lipomodel*.ti,ab,kf. or lipofill*.ti,ab,kf. or (fat* adj3 (autolog* or autotransplant* or transplant* or graft* or transfer* or inject* or infiltrate*)).ti,ab,kf. or reverse expan*.ti,ab,kf. | 13328 |
| 2 | exp Breast Neoplasms/ or exp Mammaplasty/ or mammaplast*.ti,ab,kf. or mammoplast*.ti,ab,kf. or mastoplast*.ti,ab,kf. or mastectom*.ti,ab,kf. or ((breast* or mamma* or ductal or lobular) adj3 (tumor* or tumour* or neoplas* or carcino* or cancer* or malign*)).ti,ab,kf. or ((breast* or mamma*) adj6 onco*).ti,ab,kf. or mammacarcin*.ti,ab,kf. or phyllo?de*.ti,ab,kf. or ((breast* or mamma*) adj3 (surg* or reconstruct*)).ti,ab,kf. or lumpectom*.ti,ab,kf. or ((breast or mamma*) adj3 (conserv* or spar* or amputat* or exision* or excision* or extirpat* or removal* or resect*)).ti,ab,kf. | 555234 |
| 3 | 1 and 2 | 1701 |
| 4 | limit 3 to yr="2013 -Current" | 1354 |
| 5 | 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) | 1114 |
| 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. | 802589 |
| 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$3)).tw. or Placebos/ or placebo*.tw. | 2832573 |
| 8 | Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.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 | 4935535 |

| | | |
|---|---|---|
| | 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] | |
| 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* 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.)) | 5884618 |
| 10 | 5 and 6 | 109 |
| 11 | (4 and 7) not 10 | 106 |
| 12 | (4 and (8 or 9)) not 10 not 11 | 521 |
| 13 | 10 or 11 or 12 | 736 |
| 14 | (autologous fat grafting for post-mastectomy pain syndrome: a systematic review and meta-analysis).m_titl. | 1 |
| 15 | (the prognosis outcomes of autologous fat transfer for breast reconstruction after breast cancer surgery: a systematic review and meta-analysis of cohort studies).m_titl. | 1 |
| 16 | 14 or 15 | 2 |
| 17 | 13 and 16 | 2 |