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Impact of postmastectomy radiotherapy on complications and results of immediate breast reconstruction

Hansson E, Brorson F, Chin, K, Hallberg H, Heiman Ullmark J, Jivegård L, Magnusson K, Olofsson Bagge R, Svanberg T, Svensson M, Strandell A

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Impact of postmastectomy radiotherapy on complications and results of immediate breast reconstruction [Effekter av strålning på komplikationer och resultat av direkt bröstrekonstruktion vid mastektomi]

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Table of contents

1. Abstract....4
2. Svensk sammanfattning – Swedish summary....5
3. Summary of Findings....8
4. Abbreviations/Acronyms....9
5. Background....10
6. Immediate breast reconstruction and radiotherapy....12
7. Objective....13
8. Methods....14
9. Results....14
10. Ethical issues....17
11. Organisational aspects....18
12. Economic aspects....18
13. Discussion....19
14. Future perspective....20
15. Participants in the project....21

Appendix 1 Search strategy, study selection and references

Appendix 2 Included studies – design and patient characteristics

Appendix 3 Excluded articles

Appendix 4 Outcome tables

Appendix 5 Ethical aspects

Appendix 6 Registered studies in Clinical Trials

1. Abstract

Background

Approximately 8000 Swedish women are diagnosed with breast cancer annually. Most breast cancers are treated with surgery: breast conserving (60%) or mastectomy (40%). Mastectomy is performed when, e.g., the tumour is large, or staged as T4 (the tumour has grown into the chest wall, the skin or both or is an inflammatory cancer) after neoadjuvant (before surgery) chemotherapy. Postmastectomy radiotherapy (PMRT) is given for tumours >5 cm and/or if axillary lymph node metastases are diagnosed, factors which are often unknown before surgery. One-stage (primary implant) or two-stage (tissue expander first) breast reconstruction is increasingly often performed as an immediate (IBR) or delayed procedure (DBR) after mastectomy. Eighty to one hundred IBR are performed annually at Sahlgrenska University Hospital (SU). Pre- or postmastectomy radiotherapy is reported to be associated with a higher rate of breast-related complications after IBR. The current policy in VGR is to avoid implant-based reconstruction when PMRT is anticipated or radiotherapy has been given previously. Although the tumour stage is different in patients who subsequently will need PMRT compared with those who will not need RT, the mastectomy and the IBR are performed in a standardised manner, allowing comparison of breast-related outcomes in this HTA-report. Radiotherapy is not an optional treatment. It is decided pre-operatively based on clinical data or post-operatively based on histopathological examination. Knowledge of results of IBR in patients who either must undergo PMRT or have no radiotherapy after mastectomy is important information during pre-operative counselling when discussing method of reconstruction.

Question at issue

Is there a difference in health-related quality of life (HRQoL), complication rates, re-operations or risk of developing capsular contraction or lymphedema when PMRT is given compared with not given (no RT) after implant/tissue expander based IBR in one or two stages?
The concepts implant and tissue expander are sometimes used interchangeably in the text, as a tissue expander also is a form of implant. In addition, there are different types of tissue expanders: temporary tissue expanders that subsequently are changed to permanent implant in a second stage and permanent tissue expanders that can be used to operate a patient in one-stage.

Methods

Two authors performed searches (September 2018) in PubMed, Embase, the Cochrane Library, CINAHL and PsycInfo, selected studies, independently assessed the abstracts and made a first selection of full-text articles. These articles were sent to all authors and inclusion was finally decided in consensus. The included studies were critically appraised, and data were extracted. When possible, data were pooled in meta-analysis using RevMan 5.2 and presented as forest plots.

Results

A total of 29 cohort studies and three case series were identified. Most cohort studies had some or serious study limitations and problems with precision while directness usually was unproblematic.

Patient satisfaction and HRQoL was reported in six cohort studies. A meta-analysis of three studies using Breast-Q (measuring satisfaction with breast-related outcomes as well as well-being) included 2586 patients and showed a small reduction in *patient satisfaction with outcome* as well as in the HRQoL domains *psychosocial* and *physical well-being* in the PMRT group, comparable with the minimally important difference.
Conclusion: PMRT compared with no RT may result in a small decrease in patient satisfaction in breast cancer patients undergoing IBR (GRADE ⊕⊕◯◯).

The frequency of implant/tissue expander loss was reported in 23 cohort studies and 3 case series and was consistently higher in PMRT patients. A meta-analysis (9289 breasts) demonstrated a pooled RR of 2.78 (95% CI 2.39 to 3.24).

Conclusion: PMRT compared with no RT probably results in a clinically significant increase of implant or tissue expander loss in breast cancer patients undergoing IBR (GRADE ⊕⊕⊕◯).

Breast-related re-operation rate was reported in eight cohort studies and was increased after PMRT in seven of these studies. A meta-analysis (2599 breasts) demonstrated a high heterogeneity between the studies and a pooled RR of 1.54 (95% CI 1.12 to 2.10).
Conclusion: PMRT compared with no RT may result in a substantial increase of re-operations in breast cancer patients undergoing IBR (GRADE ⊕⊕◯◯).

Pain and capsular contracture Capsular contracture rate, but not pain, was reported in 15 cohort studies and two case series and was consistently higher in PMRT patients. A meta-analysis (3866 breasts) demonstrated a high heterogeneity between the studies and a pooled RR of 3.52 (95% CI 2.15 to 5.76)
Conclusion: PMRT compared with no RT may result in a significantly increased capsular contracture rate in breast cancer patients undergoing IBR (GRADE ⊕⊕◯◯).

Overall complication rates were reported in 20 cohort studies and one case series. Reporting was not standardized and for PMRT breast cancer patients the frequency of overall complications varied from 18 to 73% compared with 12 to 60% without RT.

Concluding remarks

This systematic review including 29 cohort studies with some or serious study limitations and three case series shows that HRQoL (Breast-Q score) may slightly decrease for breast cancer patients undergoing immediate breast reconstruction receiving PMRT compared with no RT (GRADE ⊕⊕◯◯). The rate of implant/tissue expander loss (GRADE ⊕⊕⊕◯) as well as reoperation and capsular contracture rates (both outcomes GRADE ⊕⊕◯◯) were statistically and clinically significantly increased for PMRT compared with no RT patients. These findings are important when informing and advising mastectomy patients when discussing method of reconstruction, especially when it is already known that the patient will undergo PMRT. Furthermore, these results suggest that IBR has to be used with caution when PMRT is anticipated. There is still a lack of high quality studies that evaluate the impact of PMRT compared with no RT on breast-related outcome of immediate implant or tissue expander based breast reconstruction after mastectomy.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Cirka 8000 svenska kvinnor diagnostiseras årligen med bröstcancer. De flesta behandlas kirurgiskt, med bröstbevarande kirurgi (60%) eller med mastektomi (borttagande av bröstet, 40%). Mastektomi görs exempelvis när tumören är stor eller klassificeras som T4 (inflammatorisk eller växer in i bröstkorg/hud) efter neoadjuvant kemoterapi (cellgift som ges före operation). Strålbehandling efter mastektomi ges för tumörer > 5 cm och/eller om lymfkörtelmetastaser i armhålan påvisas, faktorer som ofta är okända vid mastektomin. Bröstrekonstruktion utförs allt oftare efter mastektomi och kan ske i direkt anslutning (IBR; immediate breast reconstruction) eller senare (DBR; delayed breast reconstruction). Bröstrekonstruktion kan vara en-stegs (primäroperation med permanent implantat) eller två-stegs (vävnadsexpander först, permanent implantat senare). På Sahlgrenska Universitetssjukhuset (SU) utförs årligen 80-100 IBR. Pre- eller postoperativ radioterapi har rapporterats ge högre frekvens av bröstrelaterade komplikationer efter IBR.
Aktuell policy i Västra Götalandsregionen är att undvika implantatbaserad IBR när strålbehandling förväntas postoperativt eller har getts tidigare. Hos patienter där behovet av post-operativ strålbehandling är okänt utförs mastektomi och IBR på standardiserade sätt, varför bröstrelaterade resultat av IBR kan jämföras i denna rapport, trots att tumörstadiet skiljer sig.

Strålterapi är inte ett valbart alternativ utan bestäms kliniskt pre-operativt eller postoperativt efter histopatologisk undersökning. Kunskap om resultaten av IBR hos patienter som måste genomgå PMRT jämfört med Ej RT efter mastektomi är viktig bakgrundsinformation vid medicinsk bedömning och preoperativ rådgivning till kvinnor vid diskussion av rekonstruktion.

Syfte

Studera om det finns det en skillnad i hälsorelaterad livskvalitet, komplikations- och reoperationsfrekvens eller risk för att utveckla kapselkontraktur eller lymfödem hos patienter som strålbehandlas (PMRT) jämfört med patienter som inte strålbehandlas (Ej RT) efter mastektomi med samtidig bröstrekonstruktion med implantat eller vävnadsexpander. Bröstrekonstruktionen kan utföras i ett eller två steg.

Metod

Systematisk litteratursökning utfördes (September 2018) i PubMed, Embase, Cochrane Library, CINAHL och PsycInfo av två författare som selekterade studier och oberoende av varandra granskade abstracts och gjorde ett första urval av artiklar att läsa i fulltext. Dessa artiklar sändes till samtliga författare och slutlig inklusion beslutades vid ett konsensusmöte. Inkluderade studier granskades kritiskt och data extraherades. När data var lämpliga för meta-analys utfördes det i RevMan 5.2.

Resultat

Totalt inkluderades 29 kohortstudier och tre fallserier med patienter som genomgått direkt bröstrekonstruktion efter terapeutisk eller profylaktisk mastektomi. De flesta kohortstudier hade vissa eller allvarliga begränsningar i studiedesign och problem med precisionen medan överförbarheten oftast var god.

Patienttillfredsställelse och HRQoL rapporterades i sex kohortstudier. Meta-analys av tre av dessa studier (2586 patienter) som använt Breast-Q (som innehåller både bröstrelaterade utfall och allmänt välmående) visade lägre score efter PMRT jämfört med Ej RT. Differensen motsvarade ungefär det som anses vara den minsta kliniskt viktiga skillnaden.
Slutsats: PMRT jämfört med Ej RT kan leda till något lägre HRQoL (GRADE ⊕⊕◯◯).

Förlust av implantat/vävnadsexpander rapporterades i 23 kohortstudier och tre fallserier och var konsekvent högre hos PMRT-patienter. Meta-analys (9289 bröst) visade RR 2,78 (95% KI 2,39 till 3,24). Slutsats: PMRT jämfört med Ej RT resulterar troligen i en kliniskt signifikant ökad frekvens av förlust av implantat/vävnadsexpander (GRADE ⊕⊕⊕◯).

Bröstrelaterade reoperationer rapporterades i åtta kohortstudier och var högre hos PMRT- jämfört med ej RT-patienter i sju av dessa studier. Meta-analys (2599 bröst) visade hög heterogenitet och RR 1,54 (95% KI 1,12 till 2,10).
Slutsats: PMRT jämfört med Ej RT kan leda till signifikant fler reoperationer (GRADE ⊕⊕◯◯).

Smärta och kapselkontraktur Smärta redovisades inte men kapselkontraktur rapporterades i 15 kohortstudier och två fallserier och frekvensen var konsekvent högre hos PMRT-patienter. Meta-analys (3866 bröst) visade hög heterogenitet och RR 3,52 (95% CI 2,15 till 5,76). Slutsats: PMRT jämfört med Ej RT kan kliniskt signifikant öka frekvensen av kapselkontraktur (GRADE ⊕⊕◯◯).

Sammanlagd komplikationsfrekvens rapporterades i 20 kohortstudier och en fallserie. Sättet att redovisa komplikationer skilde sig avsevärt mellan studierna. För PMRT rapporterades en komplikationsfrekvens på18-73% och för Ej RT på 12-60%.

Sammanfattande slutsats

Denna systematiska översikt inkluderade 29 kohortstudier samt tre fallserier med patienter som genomgått terapeutisk eller profylaktisk mastektomi med direkt bröstrekonstruktion och som strålbehandlats respektive ej strålbehandlats postoperativt. Kohortstudierna hade vissa eller allvarliga problem med studiedesign och precision. Tre studier visade att HRQoL kan vara något lägre hos patienter som strålbehandlas jämfört med de som inte strålbehandlas (GRADE ⊕⊕◯◯). Frekvensen av förlust av expander/implantat är troligen kliniskt signifikant högre (GRADE ⊕⊕⊕◯) och frekvensen av reoperation och kapselkontraktur (GRADE ⊕⊕◯◯ för båda utfallen) kan vara högre hos strålbehandlade patienter. Fynden är betydelsefulla för medicinsk bedömning och information till patienter avseende bröstrekonstruktion vid mastektomi, speciellt om det redan vid mastektomin är känt att patienten ska strålbehandlas postoperativt. Fynden motiverar försiktighet med direkt bröstrekonstruktion om strålbehandling efter mastektomin är aktuellt eller oklart. Sammanfattningsvis saknas det högkvalitativa studier som utvärderar bröstrelaterat resultat av implantat- eller expanderbaserad bröstrekonstruktion som utförs samtidig som mastektomi hos patienter som strålbehandlas respektive ej strålbehandlas postoperativt.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

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Head of HTA-centrum of Region Västra Götaland, Sweden, April 24 2019

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of Findings

Outcomes	Study design Number of studies	Relative effect RR (95%CI)	Absolute effect Radiation vs no radiation	Certainty of evidence GRADE[1]
HRQoL including Patient satisfaction	6 cohort studies (3 reporting Breast-Q)	-	Breast Q: *Satisfaction with outcome:* Mean difference -4.99 95% CI -5.88 to -4.11 *Psychosocial well-being:* Mean difference -6.72 95% CI -9.20 to -4.25 *Physical well-being:* Mean difference -6.67 95% CI -6.93 to -4.42	⊕⊕◯◯
Implant or tissue expander loss	23 cohort studies	2.78 (2.39 to 3.24)	19.4% vs 6.9%[3]	⊕⊕⊕◯[2]
Reoperation	8 cohort studies	1.54 (1.12 to 2.10)	41.1% vs 20.1%[3]	⊕⊕◯◯
Capsular contracture	15 cohort studies	3.52 (2.15 to 5.76)	30.2% vs 6.0%[3]	⊕⊕◯◯
Complications overall	20 cohort studies	-	Range 18-73% vs 12-60%	-

[1] Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[2] Upgraded one level due to large effect.
[3] Calculated on crude numbers in the studies included in the meta-analysis.

4. Abbreviations/Acronyms

ADM	Acellular dermal matrix
DBR	Delayed breast reconstruction
DIEP	Deep inferior epigastric perforator flap
HRQoL	Health Related Quality of Life
IBR	Immediate breast reconstruction
LD	Latissimus dorsi flap
NAC	Nipple-areola complex
NSM	Nipple sparing mastectomy
MDT	Multidisciplinary team
PMRT	Postmastectomy radiotherapy
PI	Permanent implant
RCT	Randomised clinical trial
RT	Radiotherapy
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SoS	Swedish National Board of Health and Welfare
SU	Sahlgrenska University Hospital
TE	Tissue expander
VGR	Region Västra Götaland

5. Background

Breast Cancer

Breast cancer is screened for, diagnosed, classified, and treated according to the national Swedish guidelines (Regionala cancercentrum, 2019). All cases are reported to the national cancer register (The Swedish National Cancer Register; Socialstyrelsen, 2017).

Today, the ten-year survival rate after breast cancer surgery is about 80% both nationally (Engholm et al. 2016) and regionally, in Region Västra Götaland. The prognosis is determined mainly by the stage of cancer at diagnosis (Socialstyrelsen, 2013).

Risk factors for development of breast cancer are mainly genetic, socio-demographic and influenced by reproductive factors, exogenous and endogenous hormones, life style factors, and breast density (Regionala cancercentrum, 2019). Carriers of certain mutations, such as the BReast CAncer gene (BRCA), have a 50-80% lifetime risk to develop breast cancer (Domchek et al. 2010).

Prevalence and incidence

Every year about 8000 women and 60 men are diagnosed with breast cancer in Sweden (Socialstyrelsen, 2017). The prevalence among Swedish women is approximately 100 000, which makes it the most common cancer form among women (Engholm et al. 2016). The incidence has doubled since 1960 (Socialstyrelsen, 2017). In Region Västra Götaland, approximately 1500 women are diagnosed with breast cancer annually. Moreover, there are also women with a genetically increased risk of developing breast cancer, to whom prophylactic mastectomy can be recommended. However, these patients will never receive radiation.

Surgical treatment of breast cancer

Most breast cancers are treated with surgical removal, either with a breast conserving operation (60%) or a mastectomy (40%). A mastectomy is performed for example when:

- the tumour is too large, in relation to the breast size, to perform a breast conserving operation
- there are contraindications to postoperative radiotherapy
- the tumour is multicentric
- the cancer is inflammatory
- the tumour is staged as T4[1] after neoadjuvant chemotherapy
- the patient has a known mutation or higher risk for breast cancer (Regionala cancercentrum, 2019).

In addition to the breast surgery axillary surgery is performed according to the national Swedish guidelines (Regionala cancercentrum, 2019).

Prophylactic risk-reducing mastectomy

Women who are carriers of gene mutations associated with a 50 to 80% lifetime risk to develop breast cancer, or who have an unknown hereditary condition, with an estimated lifetime risk to develop breast cancer of >25% are offered prophylactic risk-reducing mastectomies (Regionala cancercentrum, 2019). Mastectomies reduce the risk of developing breast cancer with at least 90% (Meijers-Heijboer et al. 2001).

[1] According to the TNM- staging system. T=tumour N=node M=metastasis. T4 means that the tumour has grown into the chest wall, the skin or both or is an inflammatory cancer.

Radiotherapy for breast cancer

According to the national Swedish guidelines (Regionala cancercentrum, 2019) postoperative radiotherapy is given when:

- breast conserving surgery has been performed
- the tumour has a diameter > 5 cm, irrespective of whether a mastectomy or breast conserving surgery has been performed
- when ≥ 1 axillary lymph node metastasis has been diagnosed

In approximately 20% of breast cancer patients undergoing mastectomy, the need for PMRT will be known before surgery and they are not primarily considered for an immediate breast reconstruction. The decision on PMRT in patients without clinically diagnosed axillary metastases, is based upon the pathology report. Approximately 15% will have a positive sentinel node and will be recommended PMRT with the current guidelines.

Breast reconstruction

The main aim of breast reconstruction is to increase the patient's HRQoL after breast cancer surgery. As a consequence of the increased incidence and survival rates, as well as a changed attitude, breast reconstructions have increased. A breast reconstruction can be performed as an immediate (IBR) or a delayed procedure (DBR), that is, in the same operation as the mastectomy or later as a separate procedure. The most frequently used techniques for breast reconstruction are implant based techniques, performed as a one- or two-staged procedure, and autologous techniques, such as latissimus dorsi flap and deep inferior epigastric perforator flap (DIEP). Most IBRs are implant based and performed in one or two stages with an implant or tissue expander. The concepts implant and tissue expander are sometimes used interchangeably in the text, as a tissue expander also is a form of implant. In addition, there are different types of tissue expanders: temporary tissue expanders that subsequently are changed to permanent implant in a second stage and permanent tissue expanders that can be used to operate a patient in one-stage.

Absolute contraindications for an immediate breast reconstruction are locally advanced breast cancer, inflammatory breast cancer, mental instability or inability to understand the impact of the reconstruction, risks and complications. Relative contraindications are obesity with BMI >30, active smoking, radiotherapy, and comorbidity that could have an effect on healing or risks that may extend time for surgery (Regionala cancercentrum, 2019).

There is a considerable risk of complications for all immediate breast reconstructions, even if PMRT is not given. For example, a Swedish study, included both radiated and non-radiated patients, (Arver et al. 2011) reported a complication rate of 52% in a cohort of 223 patients from eight different centres. The most common complication was partial skin necrosis (30%), followed by wound infection (17%), blood loss requiring transfusion (9%), hematoma (8%), seroma (8%), and wound rupture (4%). Serious non-breast related complications occurred in 3% of the women and the rate of implant loss was 10%. Some complications appear late after the primary surgery. For example, capsular contraction can develop years after the initial breast reconstruction. The mechanism of capsular contraction formation is not fully understood, but it is thought to be caused by a local excessive formation of collagen due to a foreign body reaction (Wolfram et al. 2004, Headon et al. 2015, Kang et al. 2018). The formation of a capsular contracture results in a firm and sometimes painful breast. The grade of capsular contraction is traditionally classified using the Baker classification system (Spear and Baker 1995).

- Grade I: a normal breast
- Grade II: a mild contraction with no symptoms
- Grade III: a moderate capsular contracture, the implant can be palpated easily and can be visible or distorted
- Grade IV: a severe firmness with significant distortion and pain

The incidence of capsular contraction varies in the literature from a few percentages to about 30%, and is the most common overall reason for reoperations and corrections (Araco et al. 2009).

Breast reconstruction in Region Västra Götaland

Annually 40-50 patients with hereditary breast cancer and 40-50 patients with diagnosed breast cancer undergo an IBR at the Sahlgrenska University Hospital. In addition, about 200 delayed breast reconstructions are performed. Immediate breast reconstruction is currently not performed in other hospitals in Region Västra Götaland.

The most common technique for IBR in Region Västra Götaland is the implant-based technique. The current policy is to avoid implant-based reconstruction in cases where postoperative radiotherapy is anticipated or radiotherapy has been given previously. Irradiated patients are reconstructed with autologous techniques.

Presents recommendations from medical societies or health authorities

According to the national Swedish guidelines (Regionala cancercentrum, 2019), a patient should be considered for immediate breast reconstruction, when a mastectomy is planned, if requested by a patient with no contraindications. There are different opinions in Sweden regarding whether radiotherapy constitutes a contraindication to implant-based IBR, but in the Swedish national guidelines for breast cancer treatment known PMRT is considered a relative contraindication due to increased risks for complications.

6. Immediate breast reconstruction and radiotherapy

In patients undergoing immediate breast reconstruction, pre- or postmastectomy radiotherapy is associated with a higher risk of breast-related complications. However, the estimated risk increase varies between studies. A Swedish study from 2013 (Eriksson et al. 2013), including 725 patients from four hospitals, found a reconstructive failure rate of 6% in non-irradiated patients, 25% in patients irradiated before mastectomy and 15% in patients receiving PMRT. The median follow-up was 43 months and an estimation of the 5-year failure rate revealed a 10% risk in the non-irradiated group, 28% in the pre-irradiated group, and 25% in the PMRT group (Eriksson et al. 2013). Similarly, Kearny et al. (2015) reported an increased risk of implant removal (26% vs 8.3%, p=0.007) and expander infection (20% vs 2.6%, p=0.001) in irradiated compared with non-irradiated patients.

Radiotherapy may also affect the patients' HRQoL and satisfaction with the reconstruction. Eriksson et al. (2013) showed that irradiated patients scored statistically significantly lower in all BREAST-Q[2] domains ($p<0.005$).

The choice between IBR and DBR has inherent difficulties since the need for PMRT is unknown preoperatively for about 80% of the patients with the present diagnostic work-up. Sentinel node examination before mastectomy would reduce the number of uncertain PMRT but would imply an additional surgical procedure.
The IBR approach has the advantage of not requiring a planned repeat surgical procedure, but about 15% of patients undergoing mastectomy will be recommended PMRT which is associated with an increased risk of local complications.

[2] The BREAST-Q, a validated PROM questionnaire, quantifies the impact of cosmetic and reconstructive breast surgery (i.e., augmentation, reduction/mastopexy, mastectomy, reconstruction, and breast conserving-therapy), pre- and post-operatively, on health-related quality of life (HR-QOL; including physical, psychosocial, and sexual well-being) and patient satisfaction (including satisfaction with breasts, outcome, and care). Each scale produces an independent score from 0–100. A higher score implies increased HRQoL and satisfaction. A value of 5 points is considered as the minimally important difference.

7. Objective

Question at issue

Is there a difference in HRQoL, complication rates, re-operations or risk of developing capsular contraction or lymphedema when postmastectomy radiotherapy* is given or not after implant or tissue expander based immediate breast reconstruction in one or two stages?

The concepts implant and tissue expander are sometimes used interchangeably in the text, as a tissue expander also is a form of implant. In addition, there are different types of tissue expanders: temporary tissue expanders that subsequently are changed to permanent implant in a second stage and permanent tissue expanders that can be used to operate a patient in one-stage.

*The radiotherapy is not optional but decided post-operatively based on the pathology report with the present diagnostic work-up. Thus, post-operative radiotherapy should not be regarded as an intervention, but rather an exposure. This report aims at describing the side-effects of radiotherapy given after mastectomy and immediate breast reconstruction, in comparison with no given radiotherapy.

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Women who undergo implant or tissue expander based immediate breast reconstruction (in one (primary implant) or two stages (tissue expander followed by secondary implant) after subcutaneous mastectomy due to breast cancer or in situ breast cancer
I	Postoperative radiotherapy
C	No radiotherapy (pre- or postoperative)
O	<u>Critical for decision making</u> HRQoL (breast related QoL)/Patient satisfaction Complications (breast related and patient related) Implant loss / reconstruction failure (breast related) Reoperation (breast related) (including conversion to an autologous reconstruction) <u>Important for decision making</u> Pain/capsular contraction Lymphedema <u>Not important for decision making</u> -

8. Methods

Systematic literature search (Appendix 1)

During September 2018 two authors (TS, KM) performed systematic searches in PubMed, Embase, the Cochrane Library, Cinahl and PsycInfo. The website of SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) and Folkehelseinstituttet (Norwegian Institute of Public Health) were also searched. Reference lists of relevant articles were scrutinised for additional references. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another and it was decided in a consensus meeting which articles should be finally included in the assessment.
Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using checklists for assessment of cohort studies from SBU. The results and the assessed quality of each article have been summarised per outcome in Appendix 4. Outcome data were extracted by at least two authors. When possible, data were pooled in meta-analysis using RevMan 5.2 and presented as forest plots. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-Findings table (page 8). The certainty of evidence was graded according to the GRADE system (Guyatt, Oxman et al. 2008).

Ongoing research

A search in Clinicaltrials.gov (2019-01-10) using the search terms *((breast OR implant) AND (reconstruction OR reconstructive OR reconstructed) OR mammaplasty OR mammoplasty OR mammaplasties OR mammoplasties) AND (immediate OR same-day OR immediately) AND (radiotherapy OR radiation OR radiated OR irradiation OR irradiated)* identified 34 trials. Sixteen were relevant for our question.

9. Results

Systematic literature search (Appendix 1)

The literature search identified 1145 articles after removal of duplicates. After reading the abstracts 981 articles were excluded. Another 81 articles were excluded by two authors after reading the articles in full text. The remaining 83 articles were sent to all participants of the project group, and 32 articles (29 cohort studies and three case series) were finally included in the assessment (Appendix 2).

Results per outcome (Appendix 4)

Patient satisfaction and HRQoL (Appendix 4.1)

Six cohort studies reported patient satisfaction and three of those reported HRQoL and patient satisfaction using Breast-Q, assessing breast related QoL. The other three studies measured similar aspects of satisfaction using different forms of questionnaires. The three studies using Breast-Q (scores 0-100) showed independently a decrease in the domain *satisfaction with outcome* in patients undergoing PMRT. All three studies applied multivariable analyses to adjust for important confounding factors. A meta-analysis including 2586 patients (Figure 1) showed a small mean reduction in Breast-Q score of 5 points, which may be regarded as the minimally clinically important difference. The other three studies used other scales and demonstrated a result in the same direction with varying degrees of reduced satisfaction after PMRT.

The three studies using Breast-Q reported the HRQoL domains to be reduced in patients undergoing PMRT compared with no RT; *psychosocial well-being* mean reduction of 6.7 points (Figure 2) and *physical well-being* mean reduction of 5.7 points (Figure 3).

Figure 1. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Patient
Outcome: Breast-Q; satisfaction with outcome

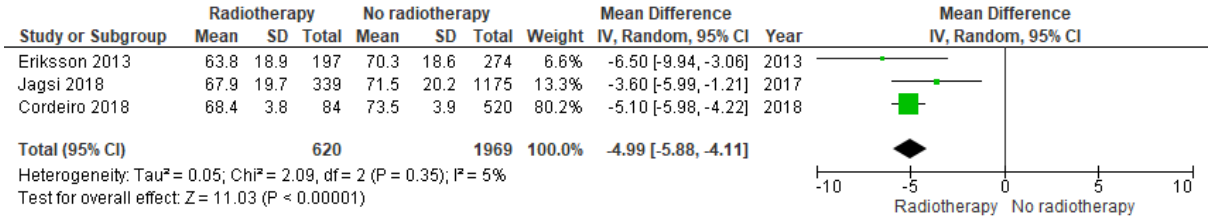


Figure 2. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Patient
Outcome: Breast-Q; psychosocial well-being

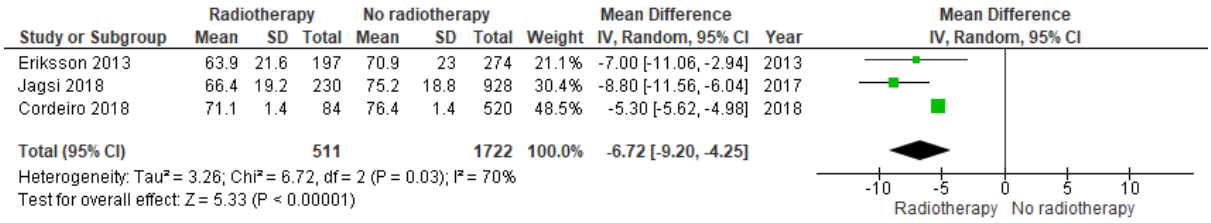
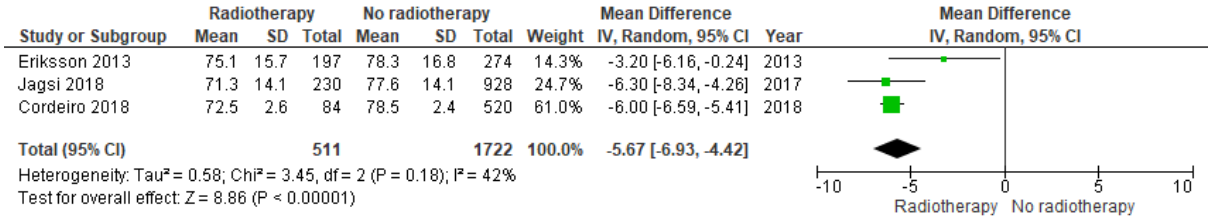


Figure 3. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Patient
Outcome: Breast-Q; physical well-being



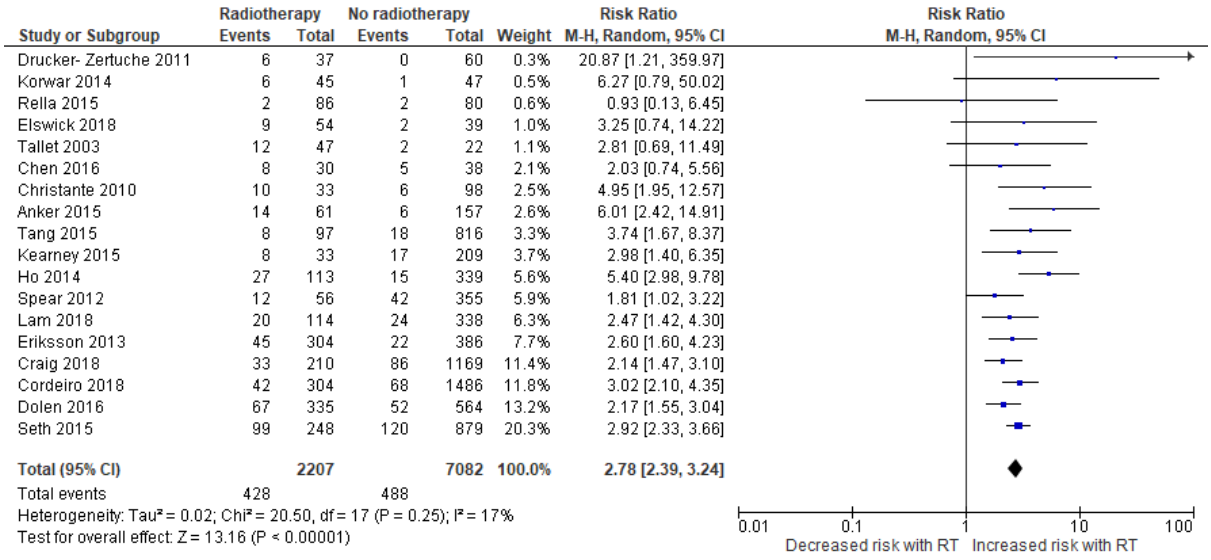
Conclusion

Post-mastectomy radiotherapy compared with no radiotherapy may result in a decrease in patient satisfaction and HRQoL in patients with breast cancer undergoing immediate breast reconstruction. Low certainty of evidence (GRADE ⊕⊕◯◯).

Implant or tissue expander loss (Appendix 4.2)

Implant/tissue expander loss was reported in 23 cohort studies and three case series and the frequency of implant or tissue expander loss was consistently higher in patients undergoing PMRT. The pooled risk ratio was 2.78 (95% confidence interval (CI) 2.39 to 3.24), including 9289 breasts (Figure 4).

Figure 4. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Breast
Outcome: Implant or tissue expander loss



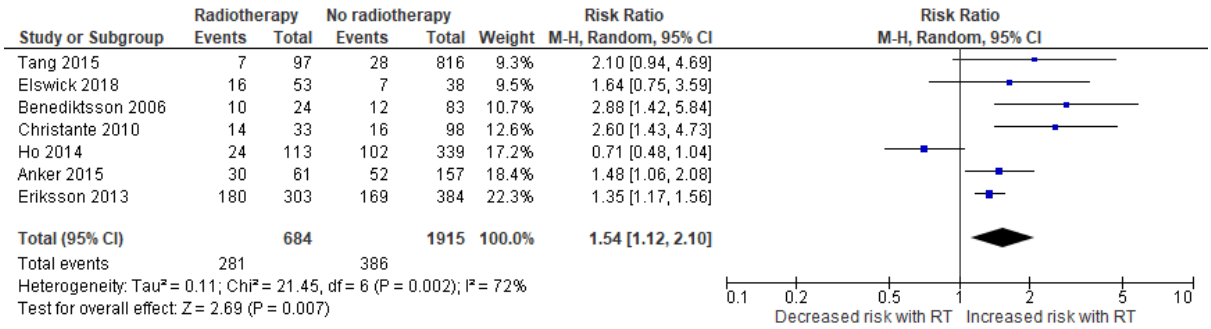
Conclusion

Post-mastectomy radiotherapy compared with no radiotherapy probably results in a more than two-fold increase of implant or tissue expander loss in patients with breast cancer undergoing immediate breast reconstruction. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Re-operations (Appendix 4.3)

Breast-related re-operations were reported in eight cohort studies and in seven of these studies an increased re-operation rate was observed after PMRT. The reasons for re-operations were infection and capsular contraction requiring implant removal as well as less severe complications like seroma and scar revision. A meta-analysis demonstrated a high heterogeneity between the studies. The pooled risk ratio was 1.54 (95% CI 1.12 to 2.10), including 2599 breasts (Figure 5).

Figure 5. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Breast
Outcome: Re-operation

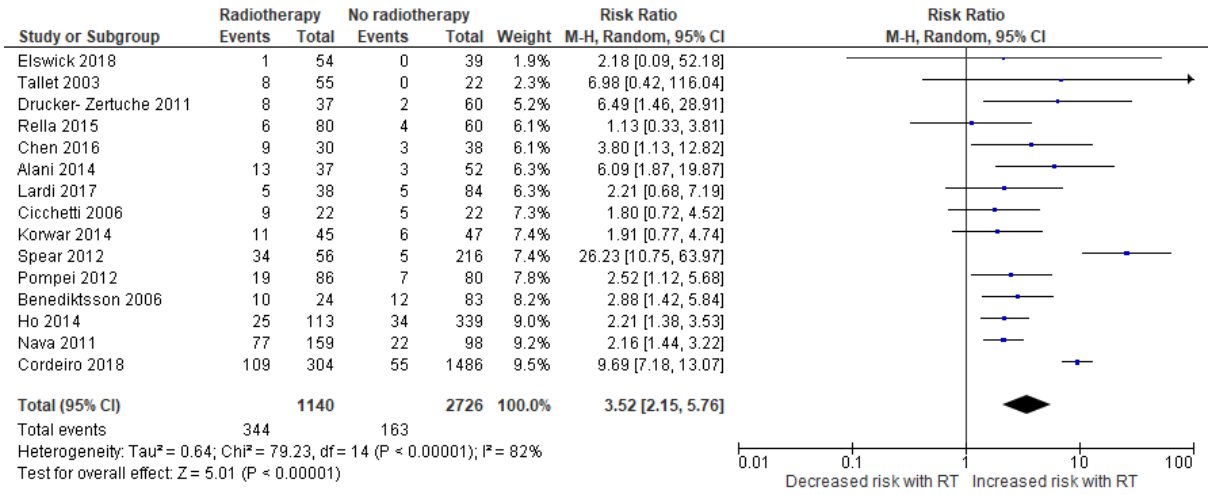


Conclusion

Post-mastectomy radiotherapy compared with no radiotherapy may result in a 50% relative increase of re-operations in patients with breast cancer undergoing immediate breast reconstruction.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Pain and capsular contracture (Appendix 4.4)
Pain was not reported in any of the included trials. Capsular contracture was analysed in 15 cohort studies and two case series. The frequency of capsular contracture was consistently higher in patients undergoing PMRT. A meta-analysis demonstrated a high heterogeneity between the studies. The pooled risk ratio was 3.52 (95% CI 2.15 to 5.76), including 3866 breasts (Figure 6).

Figure 6. Meta-analysis of studies comparing PMRT with no RT
Unit of analysis: Breast
Outcome: Capsular contracture



Conclusion
Post-mastectomy radiotherapy compared with no radiotherapy may result in a more than three-fold increase of capsular contracture rate in patients with breast cancer undergoing immediate breast reconstruction. Low certainty of evidence (GRADE ⊕⊕◯◯).

Overall complications (Appendix 4.5)
Overall complication rates were reported in 20 cohort studies and one case series. Reporting standards were heterogenous. For patients undergoing PMRT the frequency of overall complications varied from 18 to 73% compared with 12 to 60% for patients with no RT. The most frequent complications were infections, skin necrosis and seroma.

Conclusion:
Complications are frequent after immediate breast reconstruction with and without PMRT.

10. Ethical issues

There is no ethical problem with giving PMRT when needed for oncological reasons. The difficult decision is at another level, namely when a decision of IBR must be taken before the need of PMRT is known. The dilemma is that in most patients, the need for PMRT is unknown at the time of surgery. Two ethical questions may be posed: In the patient group with unknown need for PMRT, is it ethical to abstain from IBR when the great majority will have a successful reconstruction? Or on the contrary, is it ethical to perform IBR when such a high rate of complications and thus additional resource use can be anticipated in a minority of patients?

A more controversial issue is whether health-care has reason to generally abstain from IBR – to avoid the complications and extra resource use resulting from PMRT. However, this is beyond this report to take a stand on.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

Post-mastectomy radiotherapy is already used both nationally and internationally in implant based immediate breast reconstruction. At SU we try to avoid implant based immediate breast reconstruction in patients that will receive PMRT. However, IBR is used in patients where the need for PMRT could not be anticipated before the operation. The different strategies of performing IBR and PMRT versus avoiding IBR when PMRT cannot be excluded is an important clinical issue but is not the scope of this report.

Present use of the technology in other hospitals in Region Västra Götaland

To our knowledge, immediate breast reconstruction is not performed in other hospitals in VGR.

12. Economic aspects

Present costs of currently used technologies

The cost per patient with (implant-based) direct reconstruction after subcutaneous mastectomy (HAC10) was approximately 108,000 Swedish kronor (SEK) in VGR in 2017, which is assumed not to differ among patients later receiving PMRT or no RT. Unfortunately, there is no specific cost data from the cost-per-patient database for autologous techniques specifically, but at the national level it has been reported that autologous reconstruction is approx. 100,000 SEK more expensive compared to implant-based reconstruction, i.e. approx. 208,000 SEK (SBU, 2011).

Expected costs per patient of IBR with no RT and after PMRT

The meta-analysis shows a weighted re-operation rate with no RT of around 27%, and with the relative risk ratio of re-operations of 1.54 after PMRT, this implies a 41% re-operation rate after PMRT. Re-operations are assumed to be done using autologous techniques after PMRT. Based on these assumptions, the expected cost per patient with no RT is 174,000 SEK, and the expected cost per patient after PMRT is 204,000 SEK. The cost per patient is thus approx. 30,000 SEK higher after PMRT compared to no RT.

However, this is a lower-bound difference in cost, because we assumed that each patient will not undergo more than one re-operation. There were no data in the systematic review carried out in this report to indicate the average number of re-operations.

Total costs with IBR

Assuming an annual patient population of 100 patients receiving IBR at Sahlgrenska University Hospital and that 15% will require PMRT, the total expected cost per patient is 178,000 SEK, and thus 17.8 million SEK for the patient population.

Available economic evaluations or cost advantages/disadvantages

Two health economic evaluation studies were identified in the systematic search for this report.
Razdan et al. (2016) compared IBR for patients requiring PMRT with no reconstruction in a US health care context and showed it to be a cost-effective option despite the higher complication rates, given the higher health-related quality of life for the patients with immediate reconstruction.
Yan et al. (2015) analysed the cost consequences of major complications after IBR and found no difference in complication costs for patients with PMRT and with no RT, i.e. if there was any complication the costs did not differ depending on radiation (although complications are more common after PMRT). The complications causing the largest cost increases were prosthetic infection and prosthetic exposure.

13. Discussion

The aim of this Health Technology Assessment was to determine the difference in HRQoL and complication rates with or without postoperative radiotherapy after implant/ tissue expander based immediate breast reconstruction. The result showed that PMRT compared with no RT may slightly decrease HRQoL measures and patient satisfaction with outcome, measured with the Breast-Q questionnaire. The rate of implant and tissue expander loss probably increases two- to threefold, reoperation may increase 1.5 times and capsular contracture may increase more than threefold when PMRT is given compared with no RT. These findings were consistent across almost all the included studies.

The overall trend in Sweden is that most women with breast cancer are treated with breast-conserving surgery. In Region Västra Götaland, the present mastectomy rate is 40%. The recent increase in use of neoadjuvant chemotherapy is likely to make even more patients suitable for breast conserving surgery. Nonetheless, there are groups of patients in whom a mastectomy is required, such as patients with a genetically increased risk for breast cancer. Hence, there will always be sub-groups of patients who are operated on with mastectomy and where an immediate breast reconstruction has to be considered.

A breast reconstruction is an operation performed with the sole aim to increase the patient's quality of life. Data from the literature are inconsistent about the effect on HRQoL of an immediate reconstruction as compared with a simple mastectomy without reconstruction (Lee et al. 2009). Moreover, patients affected by serious complications and unplanned re-operations are significantly less satisfied and less likely to choose immediate breast reconstruction again (Boughey et al. 2015). As PMRT seems to give a lower satisfaction with outcome as well as more complications in the context of implant-based immediate breast reconstruction, the IBR method has to be used with caution in this population. The delayed reconstruction alternative for patients undergoing PMRT implies autologous reconstruction. In a two-year follow-up comparison among irradiated patients, major complications and reconstructive failures were more common after implant based (33.2% and 18.7%) than after autologous reconstruction (17.6% and 1.0%), (Jagsi et al. 2018). However, in patients not undergoing RT, major complications were less common after implant based compared with autologous reconstruction (15.6% vs 22.9%), highlighting the need for improved prediction of PMRT.

Even though the quality of the included studies was generally low, there was a consistently worse outcome when PMRT is given. This is important information when making medical decisions and informing patients when discussing method of reconstruction. The increased risk of complications and ultimately implant loss as well as the risk of a slightly lower quality of life affect both the patient and the healthcare system. The magnitude of the effects in the long-term needs to be established by future research.

A wider perspective than the focused question of this report, is how the long-term results are affected when IBR is compared with DBR. There are few studies comparing long-term outcomes with immediate versus delayed breast reconstruction in patients undergoing postmastectomy radiotherapy. We could not find any ongoing randomised clinical trials examining this question. The only ongoing trial we could find compares immediate delayed reconstruction vs. delayed reconstruction. In immediate delayed breast reconstruction, a temporary implant/tissue expander is placed before PMRT and then exchanged to an autologous reconstruction after the RT. The risks, effects and cost of such a strategy has not been evaluated.

14. Future perspective

Scientific knowledge gaps

There is a lack of high-quality studies that evaluates the results of immediate implant-based breast reconstruction in patients with PMRT compared with no RT. Only an observational design can be applied to this research question since RT is not an optional intervention. Long term effects on patients' quality of life and health need to be addressed.

To enable a more appropriate selection of patients to IBR future studies should focus on:

- Improve prediction for need of PMRT

Other important research questions are:

- Improve the IBR technique to reduce complications
- Identify risk factors for complications following IBR

Ongoing research (Appendix 6)

The search in Clinicaltrials.gov 2019-01-10 identified 34 trials. Sixteen of them were relevant for the question at issue. Among the 16, one was terminated (NCT02055937) and two were completed (NCT00473122 in 2016 and NCT01914653 in 2018) but not yet published. There were six RCTs (two, NCT02831426 and NCT02830685, constitute part I and II of the same study), three cohort studies with control groups and four case series.

Two studies (NCT03730922, NCT01664091) focus on immediate delayed breast reconstruction. One of the studies is currently recruiting and the other one is not yet recruiting.

Six studies focus on different radiotherapy regimes such as hypofractional vs conventional radiotherapy (NCT03422003 and NCT03414970), timing of radiotherapy (NCT03743324), nipple-areola-complex radiotherapy (NCT01208974) and chest wall radiotherapy (NCT03101683). The studies are currently recruiting or not yet recruiting.

Three studies compare the effect of different acellular dermal matrices/meshes in the context of radiotherapy (NCT02608593, NCT02831426, NCT02830685). The studies are not yet recruiting or have an 'unknown' status.

Two studies compare the effect of chemotherapy (NCT03627988, NCT02679040) and one of dimethyl sulfoxide (NCT02206477). Only one of the studies is currently recruiting.

None of the 13 studies described above compare radiotherapy vs. no radiotherapy as a main objective.

15. Participants in the project

The question was nominated by
Anna Elander, MD, Professor, Head of the Department of Plastic and Reconstructive Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

Participating health care professionals
Fredrik Brorson, MD
Håkan Hallberg MD, PhD
Emma Hansson MD, PhD, Associate professor
all from the Department of Plastic and Hand Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden
Kian Chin, MD
Jenny Heiman Ullmark, MD
Roger Olofsson Bagge, MD, PhD, Associate professor
All from the Department of General Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

Participants from the HTA-centrum
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Lennart Jivegård, MD, PhD, Assistant professor, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Kajsa Magnusson, HTA-librarian, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden
Therese Svanberg, HTA-librarian, Medical Library, Sahlgrenska University Hospital Gothenburg, Sweden
Mikael Svensson, professor, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden, responsible for the economic section.

Administrative support
Pernilla Brown, project coordinator, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden

External consultant
Lars Sandman, professor, Linköping University, Linköping, Sweden, contributed to the ethical section.

External reviewers
Michael Breimer, MD, PhD, Professor/Consultant surgeon, Dept of Surgery, Sahlgrenska Academy at University of Gothenburg, Sweden
Andreas Hallqvist, MD, PhD, Dept of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden

Declaration of interest
J Heiman Ullmark declares having received a speaker honorarium from Roche.
R Olofsson Bagge declares having received research grants from Astra Zeneca, speaker honorarium from Roche and Pfizer and has served on advisory boards for Amgen, BMS and MSD.
None of the other authors or the external reviewers has anything to declare.

Project time
HTA was accomplished during the period of 2018-09-03 – 2019-04-24.
Literature searches were made in September 2018.

Appendix 1: PICO, study selection, search strategies, and references

Question at issue:
Is there a difference in HRQoL, complication rates, re-operations or risk of developing capsular contraction or lymphedema when postmastectomy radiotherapy* is given or not after implant or tissue expander based immediate breast reconstruction in one or two stages?

*The radiotherapy is not optional but decided post-operatively based on the pathology report with the present diagnostic work-up. Thus, post-operative radiotherapy should not be regarded as an intervention, but rather an exposure. This report aims at describing the side-effects of radiotherapy given after mastectomy and immediate breast reconstruction, in comparison with no given radiotherapy.

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Women who undergo implant or tissue expander based immediate breast reconstruction (in one (primary implant) or two stages (tissue expander followed by secondary implant) after subcutaneous mastectomy due to breast cancer or in situ breast cancer
I	Postoperative radiotherapy
C	No radiotherapy (pre- or postoperative)
O	<u>Critical for decision making</u> HRQoL (breast related QoL)/Patient satisfaction Complications (breast related and patient related) Implant loss / reconstruction failure (breast related) Reoperation (breast related) (including conversion to an autologous reconstruction) <u>Important for decision making</u> Pain/capsular contraction Lymphedema <u>Not important for decision making</u> -

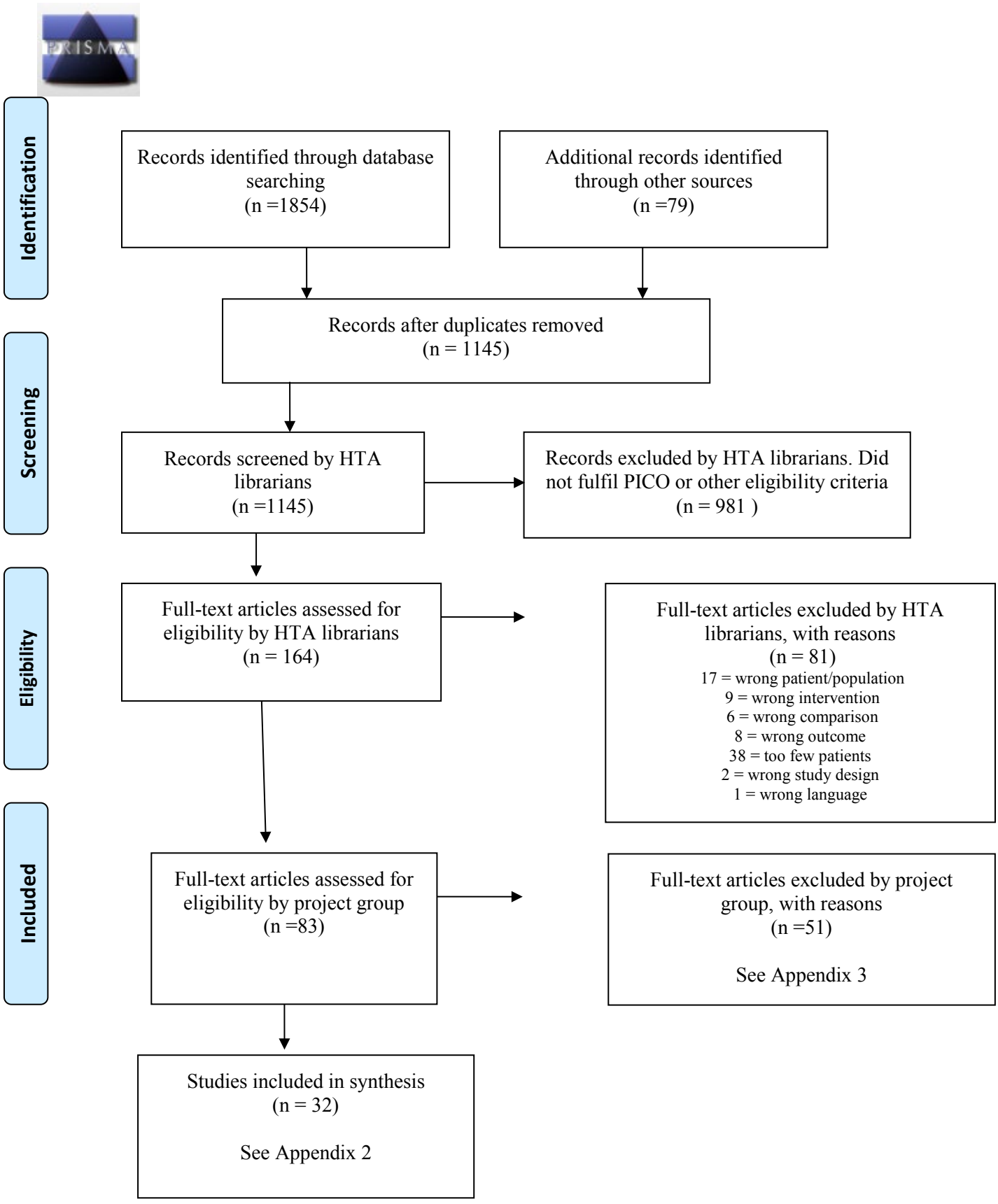
<u>Eligibility criteria</u>

Study design:
Systematic reviews (2017)
Randomised controlled trials
Cohort studies with at least 20 patients in each group
Case series (> 200 patients)
Qualitative studies

The rate of prophylactic surgery must be reported, < 20% of included patients without cancer in either breast.For complications, unilateral reconstructions can be compared to bilateral reconstructions

Language:
English, Scandinavian
Publication date:
1998-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 10 Sep 2018
No of results: 782

Query	Search	Results
#14	**Search #10 NOT #11 Filters: Swedish; Norwegian; Danish; English**	**782**
#13	Search #10 NOT #11 Filters: Publication date from 1998/01/01	842
#12	Search #10 NOT #11	926
#11	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1654955
#10	Search #8 NOT #9	951
#9	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4493104
#8	Search #3 AND #4 AND #7	958
#7	Search #5 OR #6	703077
#6	Search radiotherap*[tiab] OR radiat*[tiab] OR irradiat*[tiab]	622168
#5	Search "Radiotherapy"[Mesh] OR "radiotherapy" [Subheading] OR "Radiation Oncology"[Mesh]	262206
#4	Search immediate[tiab] OR immediately[tiab] OR same day[tiab]	381921
#3	Search #1 OR #2	36315
#2	Search Mammaplasty[mesh] OR mammoplast*[tiab] OR mammaplast*[tiab]	13322
#1	Search (breast[tiab] OR implant*[tiab]) AND (reconstruct*[tiab] OR Reconstructive Surgical Procedures[Mesh:NoExp])	29222

Database: Embase 1974 to 2018 September 7 (OvidSP)
Date: 10 Sep 2018
No of results: 931

#	Searches	Results
1	(breast or implant$).ab,kw,ti.	986025
2	reconstruct$.ab,kw,ti.	309744
3	reconstructive surgery/	5004
4	2 or 3	311254
5	1 and 4	37075
6	breast reconstruction/	14686
7	(mammoplast$ or mammaplast$).ab,kw,ti.	4300
8	5 or 6 or 7	44381
9	(immediate or immediately or same day).ab,kw,ti.	502565
10	exp radiotherapy/	453665
11	exp cancer radiotherapy/	203137
12	exp breast radiotherapy/	1215
13	radiotherapy.fs.	292002
14	(radiotherap* or radiat* or irradiat*).ab,kw,ti.	757967
15	10 or 11 or 12 or 13 or 14	950629
16	8 and 9 and 15	1640
17	(animal not (animal and human)).sh.	1007572
18	16 not 17	1636
19	limit 18 to (article or article in press or conference paper or note or "review" or short survey)	1098
20	limit 19 to (embase or medline)	1092
21	**limit 20 to ((danish or english or norwegian or swedish) and yr="1998 -Current")**	**931**

Database: The Cochrane Library (Wiley)
Date: 10 Sep 2018
No of results: 76*
Cochrane reviews: 18
Cochrane Protocols: 0
Trials: 58
Editorials: 0
Special Collections: 0
Clinical answers: 0
Other reviews: 0

*This is the number of results retrieved from two searches. The first one, #3 below, was used to retrieve results from the databases Cochrane reviews, Cochrane Protocols, Editorials, Special collections, Clinical Answers and Other reviews. Then, additional terms (#4 and #5) were added to the search in order to retrieve results from Clinical trials (#6).

#	Searches	Results
#1	(((breast OR implant*) AND reconstruct*)):ti, ab, kw	1289
#2	(mammaplast* OR mammoplast*):ti, ab, kw	355
#3	#1 OR #2	1467
#4	(immediate OR immediately OR (same day)):ti, ab, kw	59856
#5	(radiotherap* OR radiat* OR irradiat*):ti, ab, kw	36700
#6	**#3 AND #4 AND #5**	**58**

Database: CINAHL, PsycInfo (EBSCOhost), Federated search
Date: 10 Sep 2018
No of results: 65

#	Searches	Results
S7	**S3 AND S4 AND S5** **Avgränsare - Publiceringsdatum: 19980101-20181231; Språk: Danish, English, Norwegian, Swedish**	**65**
S6	S3 AND S4 AND S5	69
S5	TI (radiotherap* OR radiat* OR irradiat*) OR AB (radiotherap* OR radiat* OR irradiat*)	38,156
S4	TI (immediate OR immediately OR (same day)) OR AB (immediate OR immediately OR (same day))	138,580
S3	S1 OR S2	2,762
S2	TI (mammoplast* OR mammaplast*) OR AB (mammoplast* OR mammaplast*)	138
S1	TI (((breast OR implant*) AND (reconstruct*))) OR AB (((breast OR implant*) AND (reconstruct*)))	2,638

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
10 Sep 2018
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 79 new records

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Reference lists

Included studies:

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Project: Immediate breast reconstruction and radiotherapy
Appendix 2 – Characteristics of included studies

Author Year Country	**Study Design (Main objective)**	**Study duration (years) Follow-up (months), Mean**	**Study Groups; Intervention vs control**	**Patients (n)**	**Breasts (n)**	**Mean Age (years)**	**Prophylactic procedures** Per patient/breast (%)	**Outcome variables (Appendix)**
Alani 2014 United Arab Emirates	Cohort (Rib cage deformities)	NR 20	PMRT vs no RT	81	89	NR	NR	Pain/capsular contracture (4.4) Overall complications (4.5)
Anker 2015 USA	Cohort (Tissue expanders vs permanent implants)	1998-2009 44 vs 38	PMRT vs no RT	218	222	50 (median)	0	HRQoL (4.1) TE/implant loss (4.2) Reoperations (4.3) Overall complications (4.5)
Benediktsson 2006 Sweden	Cohort (Radiation vs no radiation in subcuntaneous implants)	1991-1994 56	PMRT vs no RT	107	107	NR	0	Reoperations (4.3) Pain/capsular contracture (4.4)
Chen 2016 USA	Cohort (Pre vs post vs no RT)	2007-2013 21 vs15	PMRT vs no RT	68	107	55 vs 50	26 breasts	TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)
Christante 2010 USA	Cohort (Predictors for complications)	1999 31 (median)	PMRT vs no RT	131	131	NR	0	TE/implant loss (4.2) Reoperations (4.3) Overall complications (4.5)
Cicchetti 2006 Italy	Cohort (Survival curves for implants)	1997-2003 60	PMRT vs no RT	44	46	48	NR	Pain/capsular contracture (4.4)
Cordeiro 2015 USA	Cohort (Timing of PMRT- one stage vs two stages)	2003-2012 30 vs 30 vs 46	PMRT vs no RT	1143	1880	46 vs 48	NR	HRQoL (4.1) TE/implant loss (4.2) Pain/capsular contracture (4.4)
Craig 2018 USA	Cohort (RT in ADM)	2004-2014 7	PMRT vs no RT	957	1376	49	NR	TE/implant loss (4.2) Overall complications (4.5)
Dolen 2016 USA	Cohort (Impact of chemotherapy)	2003-2013 29.5 (median)	PMRT vs no RT	899	1355	50	NR	TE/implant loss (4.2)
Drucker-Zertuche 2011 Mexico	Cohort (Timing of reconstruction)	2002-2008 39	PMRT vs no RT	97	97	41 vs 40 (median)	0	TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)

Project: Immediate breast reconstruction and radiotherapy
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Elswick 2018 USA	Cohort (Prepectoral implants)	2012-2016 19	PMRT vs no RT	54	93	48	39 breasts?	TE/implant loss (4.2) Reoperations (4.3) Pain/capsular contracture (4.4) Overall complications (4.5)
Eriksson 2013 Sweden	Cohort (RT in implants)	2007-2011 43	PMRT vs no RT	NR	690	46 vs 50	0	HRQoL (4.1) TE/implant loss (4.2) Reoperations (4.3)
Ho 2014 Canada	Cohort (RT in two-stage tissue expanders)	1998-2001 37 vs 44	PMRT vs no RT	312	452	46 vs 47	181 breasts (40%)	TE/implant loss (4.2) Reoperations (4.3) Pain/capsular contracture (4.4) Overall complications (4.5)
Jagsi 2018 USA	Cohort (Impact of RT)	2012-2015 NR >12	PMRT vs no RT	1247	NR	NR	NR	HRQoL (4.1) TE/implant loss (4.2) Overall complications (4.5)
Kearney 2015 USA	Cohort (Timing of RT)	2007-2013 19.6	PMRT vs no RT	188	242	51 vs 47	NR	TE/implant loss (4.2) Overall complications (4.5)
Korwar 2014 UK	Cohort (PMRT vs no RT)	2006-2011 20 (median)	PMRT vs no RT	85	109	50 vs 52	7/109 (6%)	HRQoL (4.1) TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)
Lam 2018 New Zealand	Cohort (Risk factors for implant loss)	1998-2010 40 vs 45	PMRT vs no RT	452	564	45.5 vs 48.5	NR	TE/implant loss (4.2) Overall complications (4.5)
Lardi 2017 UK	Cohort (Capsular contracture in XRT and ADM)	2008-2012 26.5 (median)	PMRT vs no RT	96	122	47.5	42/122 (34%)	Pain/capsular contracture (4.4) Overall complications (4.5)
Mendenhall 2015 USA	Cohort (Comparison of two different ADMs)	2008 – 2011 NR	PMRT vs no RT	128	199	47	Nearly 50%	TE/implant loss (4.2) Overall complications (4.5)
Nava 2011 Italy	Cohort (Timing of RT)	2003-2007 50 (median)	PMRT vs no RT	257	257	49	0	HRQoL (4.1) TE/implant loss (4.2) Pain/capsular contracture (4.4)

Project: Immediate breast reconstruction and radiotherapy
Appendix 2 – Characteristics of included studies

Author Year Country	**Study Design (Main objective)**	**Study duration (years) Follow-up (months), Mean**	**Study Groups; Intervention vs control**	**Patients (n)**	**Breasts (n)**	**Mean Age (years)**	**Prophylactic procedures** Per patient/breast (%)	**Outcome variables (Appendix)**
Peled 2012 USA	Cohort (Impact of ADM)	2006-2010 25.5	PMRT vs no RT	261	423	46.5	183/423 (43%)	TE/implant loss (4.2) Reoperations (4.3)
Pompei 2012 Italy	Cohort (PMRT in polyurethane implants)	2002-2008 51 (median)	PMRT vs no RT	166	166	58	0	Pain/capsular contracture (4.4)
Rawlani 2011 USA	Cohort (Outcome of ADM)	NR NR	PMRT vs no RT	84	121	50.2	31 / 121 (26%)	Overall complications (4.5)
Rella 2015 USA	Cohort (MRI findings)	2012-2014 9 vs 10	PMRT vs no RT	140	144	46	NR	TE/implant loss (4.2) Pain/capsular contracture (4.4)
Seth 2015 USA	Cohort (Immediate vs delayed reconstruction)	1999-2008 NR	PMRT vs no RT	834	1127	48.6	NR	TE/implant loss (4.2) Overall complications (4.5)
Spear 2012 USA	Cohort (Timing of PMRT)	2004-2010 15.2 (median)	PMRT vs no RT	272	NR	46.1	NR	TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)
Tallet 2003 France	Cohort (Effect of XRT)	1999-2000 25 (median)	PMRT vs no RT	71	NR	51.5	NR	TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)
Tang 2015 USA	Cohort (Effect of RT)	2007-2013 22 vs 23	PMRT vs no RT	NR	891	46	About 50%	TE/implant loss (4.2) Reoperations (4.3) Overall complications (4.5)
Woo 2016 Korea	Cohort (Risk factors for complications in non-obese patients)	2010-2014 NR	PMRT vs no RT	367	397	43.6	NR	TE/implant loss (4.2) Overall complications (4.5)
Ayoub 2017 USA	Case series (Evaluation of two-stage approach)	2002-2013 67	PMRT	364	384	44 (median)	0	TE/implant loss (4.2) Pain/capsular contracture (4.4)
Chetta 2017 USA	Case series (Morbidity in radiated patients)	2009-2013 NR (>15)	PMRT	3846	NR	NR	NR	TE/implant loss (4.2) Pain/capsular contracture (4.4) Overall complications (4.5)

Project: Immediate breast reconstruction and radiotherapy
Appendix 2 – Characteristics of included studies

Author Year Country	**Study Design (Main objective)**	**Study duration (years) Follow-up (months), Mean**	**Study Groups; Intervention vs control**	**Patients (n)**	**Breasts (n)**	**Mean Age (years)**	**Prophylactic procedures** Per patient/breast (%)	**Outcome variables (Appendix)**
Hirsch 2014 USA	Case series (RT in tissue expanders)	1998-2008 33	PMRT	237	240	47	0	TE/implant loss (4.2

ADM= acellular dermal matrix
HRQoL= Health Related Quality of Life
IBR= immediate breast reconstruction
MRI= magnetic resonance imaging
No RT = no radiation
NR = Not reported
PMRT= post mastectomy radiation
RT= radiotherapy
TE= Tissue expander

Project: Immediate breast reconstruction and radiation
Appendix 3: Excluded articles

Author, year	Reason for exclusion
Albornoz, 2014	Outcome not specified for intervention / control
Benediktsson, 2008	No relevant outcomes
Clarke-Pearson, 2016	Population unclear, outcome not specified for intervention / control
Cohen, 2015	Outcome not specified for intervention / control
Colwell, 2014	Population >20% prophylactic surgery, Outcome not specified for intervention / control
Cordeiro, 2004	Excluded, double publication
Cordeiro, 2014	Excluded, double publication
Crosby, 2012	Population >20% prophylactic surgery, Outcome not specified for intervention / control
Eriksen, 2011	Outcome not specified for intervention / control
Fairchild, 2018	Outcome not specified for intervention / control
Fisher, 2014	Outcome not specified for intervention / control
Franchelli, 2015	Outcome not specified for intervention / control
Haffty, 2016	Outcome not specified for intervention / control
Hansen, 2018	Outcome data not extractable
Henderson, 2014	Population too wide, incl mastectomy alone, wrong control
Ibrahim, 2013	Outcome not specified for intervention / control
Jagsi, 2016	Population too wide, incl mastectomy alone
Kelsall, 2017	Population wrong, control wrong
Kern, 2015	Population wrong
Khavanin, 2013	Outcome not specified for intervention / control
Magill, 2017	Systematic review with all relevant articles included in our review
Myckatyn, 2015	Irrelevant outcome
Nice guideline, 2018	Systematic review with all relevant articles included in our review
Olsen, 2017	Complications not reported for the right population subgroup
Peled, 2014	Not reported for RT vs non-RT, case series too small for RT
Pu, 2018	Systematic review with all relevant articles included in our review
Rancati, 2013	Outcome not specified for intervention / control
Razdan, 2016	Incorrect control, outcome not presented for RT vs non-RT, too small as case series (cost)
Reisch, 2013	Populaton unclear, intervention not specified for pre- or postop RT
Reish, 2015	Population unclear, outcome missing
Ricci, 2016	Population unclear, intervention mixed pre- and postop RT
Robertson, 2012	Outcome not specified for intervention / control
Roh, 2017	Control includes side without breast cancer
Saha, 2013	Wrong intervention
Salibian, 2017	Case series with too few patients, mixed intervention pre- and postop-RT
Salzberg, 2016	Population majority not breast cancer
Sandberg, 2017	Missing relevant outcomes

Project: Immediate breast reconstruction and radiation
Appendix 3: Excluded articles

Author, year	Reason for exclusion
Sandelin, 2004	Case series with too few patients, no comparison between Intervention and Control
Sbitany, 2017	Population unclear, breast cancer vs prophylactic (40% prophylactic)
Sbitany, 2014	Population unclear. Proportion of breast cancer patients not reported
Scheflan, 2018	Population unclear. Proportion of breast cancer patients not reported
Seth, 2012	Excluded, double publication
Sinha, 2017	Population >20% prophylactic surgery, unclear percentage of prophylactic surgery
Wang, 2015	Population >40% prophylactic surgery
Warren, 2012	Missing relevant outcomes
Wengler, 2017	Data for post-mastectomy RT and no RT reported separately
Wilkins, 2018	Population unclear portion of prophylactic, unclear intervention
Wu, 2018	Missing relevant outcomes
Yan, 2015	Missing relevant outcomes (cost)
Zhao, 2018	Population wrong
Zhu, 2016	Population case series with too few patients

RT = Radiotherapy

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.1
Outcome variable: HRQoL including Patient satisfaction

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= (RT vs no RT)	Response rate	Results		Comments	Directness *	Study limitations *	Precision *
				Radiotherapy Mean (SD)	**No radiotherapy** Mean (SD)				
Anker 2015 USA	Cohort	145 (39 vs 110 breasts)	149/222 breasts (67%)	Satisfaction with breast reconstruction Agree (n=20) 51% Neutral (n=7) 18% Disagree (n=12) (31%)	Satisfaction with breast reconstruction Agree (n=60) 55% Neutral (n=15) 14% Disagree (n=35) (32%)	In-house questionnaire with a 5-point Likert Scale. The answers are given as a 3-point scale. p-values are not given	+	?	-
Cordeiro 2015 USA	Cohort	626 (106 vs 520)	626/1143 (55%)	Satisfaction with outcome With expander (n=22) 70.2 (3.0) With implant (n=84) 68.4 (3.8) Psychosocial well-being With expander (n=22) 72.3 (1.2) With implant (n=84) 71.1 (1.4) Physical well-being With expander (n=22) 73.4 (1.9) With implant (n=84) 72.5 (2.6)	Satisfaction with outcome With expander/implant (n=520) 73.5 (3.9) p<0.01 Psychosocial well-being With expander/implant (n=520) 76.4 (1.4) p<0.001 Physical well-being With expander/implant (n=520) 78.5 (2.4) P<0.001	Postoperative Breast-Q (0-100, a higher value indicates a better result. MID 5 points). The scores are given as medians and SDs. The scores have been adjusted for BMI, laterality and follow-up.	+	?	+
Eriksson 2013 Sweden	Cohort	471 (197 v s 274)	471/690 (68%)	Satisfaction with outcome 63.8 (18.9) Psychosocial well-being 63.9 (21.6) Physical well-being 75.1 (15.7)	Satisfaction with outcome 70.3 (18.6) p<0.001 Psychosocial well-being 70.9 (23.0) p<0.001 Physical well-being 78.3 (16.8) p=0.005	Postoperative Breast-Q (2 months postoperatively). 0-100, a higher value indicates a better result. MID 5 points). The statistical comparison is performed for PMRT (prior or postoperatively) vs No RT.	+	+?	+?

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.1
Outcome variable: HRQoL including Patient satisfaction

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= (RT vs no RT)	Response rate	Results		Comments	Directness *	Study limitations *	Precision *
				Radiotherapy Mean (SD)	**No radiotherapy** Mean (SD)				
Jagsi 2018 USA	Cohort	1514 (339 vs. 1175)	1514/1604 (94%) at 1 year and 1158/1604 (72%) at 2 years	Satisfaction with outcome 1 year: (n=339) 67.9 (19.7) 2 years: (n=230) 64.8 (22) Psychosocial well-being 1 year: (n=339) 66.7 (18.5) 2 years: (n=230) 66.4 (19.2) Physical well-being 1 year: (n=339) 70 (13.8) 2 years: (n=230): 71.3 (14.1)	Satisfaction with outcome 1 year: (n=1175) 71.5 (20.2) p=0.008 2 years: (n=928): 71.3 (21.4) p=002 Psychosocial well-being 1 year: (n=1175) 72.6 (19.2) 2 years: (n=928): 75.2 (18.8) Physical well-being 1 year: (n=1175) 77.1 (14.1) 2 years: (n=928): 77.6 (14.1)	Postoperative breast-Q (1 and 2 years postoperatively). 0-100, a higher value indicates a better result. MID 5 points. P-values not given for psychosocial and physical well-being.	+	?	-?
Korwar 2014 UK	Cohort	63	63/83 (76%)	General appearance 3.35 Appearance of breast 3.5	General appearance 4.08 p=0.02 Appearance of breast 4.06 p=0.06	Postoperative Breast Evaluation Questionnaire (BEQ) and "supplementary questions relevant to the study". Outcomes were scored on a scale of 1-5, where 1 is "poor" and 5 is "excellent". The cohort includes 6 women who have had previous RT and 1 who had previous mantel RT. HRQoL data is not given separately for these patients.	-	-	-
Nava 2011 Italy	Cohort	207 (116 vs 91)	207/257 (81%)	Rating of final result Good (n=59)51% Medium (n=45) 39% Bad (n=12) 10%	Rating of final result Good (n=62) 68% Medium (n=27) 30% Bad (n=2) 2% p=0.04	Patients were asked to rate their reconstructions as "good", "medium" or "bad".	+	?-	?

HRQoL = Health related quality of life, MID = Minimally important difference, No RT = No radiotherapy, PMRT = Post mastectomy radiotherapy

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.2
Outcome variable: Implant or tissue expander loss/reconstruction failure

* + No or minor problems
? Some problems
- Major problems

Author year country	**Study design**	**Number of patients** (n= RT vs No RT) **and/or breasts**	**Lost to follow up (n)**	**Length of follow up,** months Mean (SD)	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
					Postmastectomy radiotherapy (RT)	**No radiotherapy (No RT)**				
Anker 2015 USA	Cohort	218 (61 vs 157)	0	44 (range 6-144)	PI loss 5y: 22.4%	PI loss 5y: 3.6% p = 0.006		+	?	?
Chen 2016 USA	Cohort	76 (30 vs 38)	0	NR	TE loss 26.3% OR 2.32 (0.65-8.32) n.s.	TE loss 13.3% n.s.		+	?	?
Christante 2010 USA	Cohort	131 (33 vs 98)	NR	Median 31 (range 1-101)	TE loss 31%	TE loss 6% p<0.005	302 included, 32 lost to follow-up, 131 immediate reconstructions, loss to follow-up not extractable	+?	?	-
Cordeiro 2015 USA	Cohort	1143 (304 vs 1486 breasts)	0	no RT 45.6 (0.3-133) TE+RT 30.1 (0.5-118) PI+RT 40.3 (1.6-113)	TE loss: 32% PI loss:16.4%	TE loss: 8.5% PI loss 1% p<0.01		+	+?	?
Craig 2018 USA	Cohort	957 (1370 breasts, 201 vs 1169)	0	7 (range 2 - 10.1)	33/210, Non-ADM OR 3.19 (1.49-6.52) p=0.002 ADM OR 1.22 (0.45-3.29) n.s.	86/1169	P-values given only for subgroups and then n.s. for RT	+	?	+?
Dolen 2016 USA	Cohort	899 (335 vs 564)	0	11.8 (range 7-20.2)	TE loss: 20% TE loss OR 1.6 (0.8-2.2) n.s.	TE loss: 15% p= 0,04		?	?	?
Drucker-Zertuche 2011, Mexico	Cohort	97 (37 vs 60)	0	Not given	TE loss: 6/37	TE loss: 0	No p-values	?	-	-
Elswick 2018 USA	Cohort	54 (93 breasts, 54 vs 39)	0	19	TE/PI loss: 16.7% (9/54) Failure 15%	TE/PI loss 5.1% (2/39) Failure 5%	No p-values	+	+	?

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.2
Outcome variable: Implant or tissue expander loss/reconstruction failure

* + No or minor problems
? Some problems
- Major problems

Author year country	**Study design**	**Number of patients** (n= RT vs No RT) **and/or breasts**	**Lost to follow up (n)**	**Length of follow up,** months Mean (SD)	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
					Postmastectomy radiotherapy (RT)	**No radiotherapy (No RT)**				
Eriksson 2013 Sweden	Cohort	725 (386 vs 304)	0	43 (range 9-73)	Failure: 15% (45/304) (5y 25,2%)	Failure: 6% (22/386) p<0.001 (5y 10,4%)		+	+	+
Ho 2014 Canada	Cohort	312 (452 breasts;113 vs 339)	0	37.3 (27.7) vs 44.2 (29.5)	Failure 23.9%	Failure 4.4%	No p-value	+	?	+
Jagsi USA 2018	Cohort	1504 (386 vs 1218)		24	(1 year failure 12.2%) (2 year failure 18.7%)	(1 year failure 3.5%) (2 year failure 3,4%)	No p-value No p-value Mixed immediate and delayed reconstructions– data not extractable for subgroups relevant to PICO			
Kearney 2015 USA	Cohort	188 (32 vs 156) (242 breasts:33 vs 209)	0	19.6 (range 3.1-68.8)	TE/PI loss: 26% Failure 21.2% RR 3.41(1.469-7.918) OR 2.735 (0.71-10.54) n.s.	TE/PI loss: 8.1%% p=0.0013 Failure 6.2%	Loss and failure rates per breast	+	?	-
Korwar 2014 UK	Cohort	92 (45 vs 47)	0	Median 20 (no range)	TE/PI loss 6/45 (13%)	TE/PI loss 1/47 (2%) n.s.		-	-	-
Lam 2018 Australia, NZ	Cohort	452 (114 vs 338) (562 breasts)	9	Median 3.3 vs 3.74 years	TE/PI loss 20/114 (17.5%) IRR 2.225 SE 0.802 p=0.0027	TE/PI loss 24/338 (7.1%)	7/114 lost pre-RT (6.1%) 11/114 lost post-RT (9.6%)	+	?	+
Mendenhall 2015 USA	Cohort	128 (52 vs 76) (199 breasts: 53 vs 146)	31	3-24	TE loss OR 1.25 n.s		Randomized ADM study, complications extracted as cohort	+	?	-
Nava 2011 Italy	Cohort	257 (159 vs 98)	0	Not given	PI loss RT on PI: 6.4% TE loss RT on TE 40%	PI loss 2.3% (p=0.0001) TE loss not given.		+	?-	?

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.2
Outcome variable: Implant or tissue expander loss/reconstruction failure

* + No or minor problems
? Some problems
- Major problems

Author year country	**Study design**	**Number of patients** (n= RT vs No RT) **and/or breasts**	**Lost to follow up (n)**	**Length of follow up,** months Mean (SD)	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
					Postmastectomy radiotherapy (RT)	**No radiotherapy (No RT)**				
Peled 2012	Cohort	288 (450 breasts; 68 vs382)	0	25.2	Consecutive ADM OR 4.87 (95%CI 0.59 to 40.1) Selective ADM: OR 6.07 (1.74 to 21.2)		OR adjusted for Age and BMI	+?	?-	?
Rella 2015 USA	Cohort	140 (80 vs 60)	0	Less than 36	PI loss 2/80	PI loss 2/60	No p-value	?	?-	-
Seth 2015 USA	Cohort	834 (208 vs 626) (1127 breasts;248 vs 879)	0	Unclear, patients recruited over 9 years	Failure 40%	Failure 13.7% p=0.04	No mean or median follow up stated, study includes all patients 1999-2008. Failures per breast.	?	?-	+?
Spear 2012 USA	Cohort	289 (428 breasts; 56 vs. 355 breasts)	17?	Median 15.2 (range 6-80.5) after stage 2	Failure: 36.7%	Failure: 11.1% p<0.0001	Authors' definition of failure differs from HTA definition (21.4% vs 11.8%). Patients included 2004-2010. 361 breasts had complete follow-up	?	?-	+?
Tallet 2003 France	Cohort	69 (47 vs 22)	0	Median 25	Failure: 26%	Failure: 9%	No p-value	+	?	-
Tang 2015 USA	Cohort	565 (982 breasts; 97 vs. 816)	0	Median 23 (range 1-76)	Failure: 8 (8%)	Failure: 18 (2%) p=0.003		+	?	?
Woo 2016 Korea	Cohort	367 (397; 63 vs. 327)	0	Unclear	Failure: OR 13 (p<0.001)		Patients included 2010-2014	+	?	?
Ayoub 2017 USA	Case series	382	7 (1.8%)	5 years	TE/PI loss 50/372 (13%)					

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.2
Outcome variable: Implant or tissue expander loss/reconstruction failure

* + No or minor problems
? Some problems
- Major problems

Author year country	**Study design**	**Number of patients** (n= RT vs No RT) **and/or breasts**	**Lost to follow up (n)**	**Length of follow up,** months Mean (SD)	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
					Postmastectomy radiotherapy (RT)	**No radiotherapy (No RT)**				
Chetta 2017 USA	Case series	2875	0	15	TE/PI loss: 27%,					
Hirsch 2014 USA	Case series	237	5	33	TE loss 14% PI loss 12.5%					

PI Permanent Implant
TE Tissue expander
RT Radiotherapy (postmastectomy radiotherapy only)
PMRT Postmastectomy radiotherapy
Loss TE or PI explanted for any reason except planned exchange
Failure of the originally planned immediate reconstruction, regardless if one- or two stage, i.e. salvage surgery with flaps is defined as failure

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.3
Outcome variable: Reoperation (breast related)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Anker 2015 USA	Cohort	218(222) (61 vs 157)	0	44 (NR) (Median 38, range 6-144)	Reoperation for surgical complications at 5y: 50%	Reoperation for surgical complications at 5y: 33%, p = 0.007	No prophylactic surgery. 37% received ADM	+	?	?
Benediktsson 2006 Sweden	Cohort	107 (24 vs 83)	13/107	Median 60(24-60)	Reoperation due to capsular contraction at 2-6y: 10/24, 41.7%	Reoperation due to capsular contraction at 2-6y: 12/83, 14.5%%	6/22 with capsular contraction was not operated on due to advanced disease but the amount from each group NR	+	?-	?
Christante 2010 USA	Cohort (Prediction of complications)	131(131) (33 vs 98)		Median 31(1-110)	Reoperation for complication: 14/33, 42,4%	Reoperation for complication: 16/98, 16.3%, p=<0.001		+?	?	-
Elswick 2018 USA	Cohort	54(93)	1 (2)	Median19(1-36)	Unplanned reoperation: 16/53 30.2%	Unplanned reoperation: 7/38 18.4%	TE and implant	+	+	?
Eriksson 2013 Sweden	Cohort	690 (304 vs 386)	NR	Median 43(9-73)	At least one unplanned reoperation: 180/303, 59%	At least one unplanned reoperation: 169/384, 44%, p<0.001		+	+	+
Ho 2014 Canada	Cohort	312(452) (113 vs 339)	NR	No RT: 44.2(29.2) PMRT: 37.3(27.7)	Revision rate : 20.9%	Revision rate : 30.2%	MORE revisions in No RT group	+	?	+
Peled 2012 USA	Cohort (Impact of ADM)	261(423) (68 vs 355)		25.5(3.3-58.9))	Unplanned reoperations: Selective ADM: OR 5.7 (CI 95% 2.33-14.1) Consecutive ADM: OR 1.42 (CI95% 0.27-7.41)	Non RT as reference		+?	?-	-
Tang 2015 USA	Cohort	565/982 97 vs 816	0	Median 23 (1-76)	Revision rate: 7.2%	Revision rate: 3.4%	Patients lost at follow-up excluded	+	?	?

ADM = Acellular Dermal Matrix
No RT = no radiation
NR = Not reported
PMRT= post mastectomy radiation

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.4
Outcome variable: Pain/capsular contracture

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Alani 2014 United Arab Emirates	Cohort	81 (89) (37 vs 52)	0	20(NR)	Pain: NR Capsular contracture grade III-IV, 35.0%	Pain: NR Capsular contracture grade III-IV, 5.7%	Unclear rate of prophylactic surgery. P values NR Prospective for chest wall deformity	?-	-	-
Benediktsson 2006 Sweden	Cohort	107(NR) (24 vs 83)	13/107	Median 60 (24-60)	Pain: NR Capsular contracture grade III-IV, 41.7%	Pain: NR Capsular contracture grade III-IV, 14.5% (p=0.01)		+	?-	?
Chen 2016 USA	Cohort	68(NR) (30 vs 38)	NR	No RT: 14.7 (12.27) PMRT: 20.87(15.31)	Pain: NR Capsular contracture grade NR, 28.9%	Pain: NR Capsular contracture grade NR 6.7%	Uncertain severity of capsular contraction	+	?	-
Cicchetti 2006 Italy	Cohort	44(46) (22 vs 22)		Median 60 (12-72)	Pain: NR Capsular contraction: 41% (all) Immediate group: 26%	Pain: NR Capsular contraction: 21%(all) Immediate group: 13%	Mixture of immediate/delayed and implant exchange with Style 150 prosthesis	?	-	-
Cordeiro 2015 USA	Cohort	1790(NR) (1486 vs 304)	NR	No RT: 45.6 (0.3-133) PMRT-TE: 30.1(0.5-118) PMRT-implant: 40.3(1.6-113)	Pain: NR Capsular contraction grade III TE: 15.9% Capsular contraction grade III implant: 44.6%	Pain: NR Capsular contraction grade III: 3.7%	Capsular contracture grade IV: 0.4% (No RT), 1.22%(TE-PMRT) and 6.3% (implant-PMRT) respectively	+	?	+?
Drucker-Zertuche 2011 Mexico	Cohort	97(97) (37 vs 60)	NR	39(4-72)	Pain: NR Capsular contracture grade III-IV: 8/37, 21.6%	Pain: NR Capsular contracture grade III: 2/60, 3.3%	p-value missing	?	-	-
Elswick 2018 USA	Cohort	54(93) (54 vs 39)	NR	19 (1-36)	Pain: NR Capsular contraction (III-IV): 1.9%	Pain: NR Capsular contraction (III-IV): 0%	Data calculated as per breast	+	+	?
Ho 2014 Canada	Cohort	312(452) (113 vs 339)	NR	No RT: 44.2 (29.2) PMRT: 37.3 (27.7)	Pain: NR Capsular contraction: 21.7%	Pain: NR Capsular contraction: 10.0%		+	?	+

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.4
Outcome variable: Pain/capsular contracture

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Korwar 2014 UK	Cohort	92(116) (45 vs 47)	NR	Median 20 (NR)	Pain: NR Capsular contraction (III-IV): 24%	Pain: NR Capsular contraction (III-IV): 13%		-	-	-
Lardi 2017 UK	Cohort	96(122) (38 vs 84 breasts)	NR	Median 26.5 (6-51)	Pain: NR Capsular contraction (III-IV): 13.2%	Pain: NR Capsular contraction (III-IV): 6.0% (p=0.216)	80/122 for oncological reasons vs 42/122 for risk-reducing reasons	?	?	-
Nava 2011 Italy	Cohort	257(NR) (159 vs 98)	NR	Median >60 (NR)	Pain: NR Capsular contraction (III-IV): 48.2%	Pain: NR Capsular contraction (III-IV): 22.4%, p<0.0001	Calculated from table: PMRT 77/159 vs No RT 22/98	+	?-	?
Pompei 2012 Italy	Cohort	166(166) (86 vs 80)	NR	51 (12-90)	Pain: NR Capsular contraction (III-IV): 21.7%	Pain: NR Capsular contraction (III-IV): 8.3%	Numbers presented for textured implants (Poly-urethane implant (6.3 vs 0%)	+?	-	-
Rella 2015 Italy	Cohort (MRI findings)	140(141) (80 vs 60)	NR	6 months (mean or median NR)	Pain: NR Capsular contraction (grade NR): 7.5%	Pain: NR Capsular contraction (grade NR): 6.7%	Evaluated by MRI as fibrous tissue around an intact implant on T"-weighted TSE image	?	?-	-
Spear 2012 USA	Cohort (Timing of PMRT)	272(NR) (56 vs 216)	NR	Median 15.2 (6-80.5)	Pain: NR Capsular contraction (III-IV): 34/56, 60.7%	Pain: NR Capsular contraction(III-IV): 5/216, 2.3%	p-value missing	+	?	?-
Tallet 2003 France	Cohort	77(NR) (55 vs 22)	NR	Median 25(19-42)	Pain: NR Capsular contraction (III-IV): 15%	Pain: NR Capsular contraction (III-IV): 0%		+	?	-
Ayoub 2017 USA	Case series	364(384)	7	67.2 (15.6-160.8)	Pain: NR Capsular contraction: 10% of failures	NR	All patients received PMRT. Capsular contraction only reported for failures(5/50)			
Chetta 2017 USA	Case series	2875(NR)	NR	15 (NR)	Pain: NR Capsular contraction: 38/2875, 8%	Pain: NR Capsular contraction: NR				

MRI = Magnetic Resonance Imaging
No RT = No radiotherapy
NR = Not reported
PMRT= Post mastectomy radiotherapy

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.5
Outcome variable: Overall complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Alani 2014 UAE	Cohort prospective for chest wall deformity	81 (89) (37 vs 52 breasts)	0	16 vs 23 (no SD)	Chest wall deformity 70.2%	Chest wall deformity 32.6%	Unclear rate of prophylactic surgery. P-values not reported	+	?	-
Anker 2015 USA	Cohort retro-spective	218 (61 vs 157)	0	44 (no SD) Median 38, range 6-144	Implant replacement 5y: 23.5% Non implant related complications: 22.5%	Implant replacement 5y: 21.3%, n.s. Non-implant related complications: 10.8% n.s.	No prophylactic surgery. 37% received ADM	+	?	?
Chen 2016 USA	Cohort	76 (38 vs 30)	0	NR	Any complication: 73%, 26/38 (68%) major, 40% minor	Any complication:60%, 14/30 (47%) major 37% n.s.	8/76 pre-RT, 38/76 PMRT. Definitions of major and minor complications provided. Matched pair analysis shows significantly higher complication rates per breast in RT group but data not extractable.	+	?	-
Christiante 2010 USA	Cohort	131 (33 vs 98)	Un-clear	Median 31 (range 1-101)	Any complication: 42%	Any complication: 16% p<0.001	No definition of complications. Rates include TE/PI loss. 302 included, 32 lost to follow up, 131 immediate reconstructions, loss to FU not extractable	+?	?	-
Craig 2018 USA	Cohort	957 (1370 breasts, 201 vs 1169))	0	7 (range 2 -10.1)	Complication (ADM): 37.4% Complication (non-ADM):15.5% OR 1.76 (1.22-2.56) p=0.0027	Complication (ADM): 47.7% p<0.0001 Complication(non-ADM): 23.9% p<0.0001	All complications are per breast. RT 69/201 (34%) vs no RT 288/1169 (24%) complication Complication rates exclude TE loss	+	?	+?
Drucker-Zertuche 2011 Mexico	Cohort	97 (37 vs 60)	0	?	Overall complications: 45.9% (17/37)	Overall complications: 11.6% (7/60)	No p-values	?	-	-

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.5
Outcome variable: Overall complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Elswick 2018 USA	Cohort	54 (93 breasts, 54 vs 39)	0	19	Any complication 25.9%	Any complication: 23.1%	No p-values	+	+	?
Ho 2014 Canada	Cohort	312 (452 breasts;113 vs 339)	0	37.3 (27.7) vs 44.2 (29.5)	Late complication: 32.9% Major complication OR 4,2 (1.4-12.7) p<0,001	Late complication: 8.3% p<0.01	Early complications without significant differences. Subgroups of complications analyzed. Definitions of complications given but data extraction not possible.	+	+?	+
Jagsi 2018 USA	Cohort	2247 (1625 vs 622)		2 years	Complications: 38.9%	Complications: 21.8%	Complications lower in autologous reconstruction than implant reconstructions with RT 40-50% bilateral	+	?	-?
Kearney 2015 USA	Cohort	210 (32 vs 156) (265 breasts:33 vs 209)	0	19.6 (range 3.1-68.8)	Any major complication 24.2% OR 2.019 (0.63-6.474) n.s.	Any major complication 11% n.s.	Complications per breast. Major complications specified.	+	-	-?
Korwar 2014 UK	Cohort	92 (45 vs 47)	0	Median 20 (no range)	Overall complication 13/45	Overall complication 17/47	No p-value for overall complication	-	-	-
Lam 2018 Australia, NZ	Cohort	452 (114 vs 338) (562 breasts)	9	Median FU 3.3 vs 3.74 yrs	Any complication 30.8%+28% (58.8%)	Any complication 31.1%+8.3% (39.4%)	Complications separated for occurrence in stage 1 or 2. No statistical analysis of overall complications.	+	?	+
Lardi 2017 UK	Cohort	96 pat (122 breasts: 38 vs 84)	0	Median 26.5 (no range)	Overall complication 12/38 BR (31.6%)	Overall complication 20/84 BR (23.8%) n.s.	Originally 149 p, 200 br, 28 had implant loss or change of method (excluded from analysis in study)	-	-	-

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.5
Outcome variable: Overall complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Mendenhall 2015 USA	Cohort	128 (52 vs 76) (199 breasts: 53 vs 146))	31	3-24	Overall complications OR 1.81 n.s.		Randomized ADM study, complications extracted as cohort	+	?	-
Rawlani 2011 USA	Cohort	84 (26 vs 95)	0	NR	Overall complication 8/26 (30.8%)	Overall complication 13/95 (13.7%)	ADM case series	+	?	-
Seth 2015 USA	Cohort	834 (208 vs 626) (1127 breasts: 248 vs 879)	0	NR	Total complication: 26.6%	Total complication: 15% p<0.0001	Includes all patients 1999-2008. Complications per breast.	+	?-	?+
Spear 2012 USA	Cohort	289 (428 breasts; 56 vs. 355 breasts)	17?	Median 15.2 (range 6-80.5) after stage 2	Stage 1 complications 8/56	Stage 1 complications 48/355 n.s.	Patients included 2004-2010. 361 breasts had complete follow-up. Complications per breast, excluding contracture and any reoperation. Data not extractable for Stage 2.	+	?	?-
Tallet 2003 France	Cohort	69 (27 vs 22)	0	Median 25	Complications: 49%	Complications: 14% p=0.01	List of specific complications provided	+	?	-
Tang 2015 USA	Cohort	565 (982 breasts; 97 vs. 816)	0	Median 23 (range 1-76)	Overall complications: 17 (18%)	Overall complications:83(10%) p=0.03		+	?	?
Woo 2016 Korea	Cohort	367 (397 breasts 63 vs. 327)	0	NR	Overall complications: OR 3.54 (1.96-6.94) (p<0.001) Major complications: OR 3.1 (1.96-5.7) (p<0.001)		Patients included 2010-2014. Complications per breast.	+?	+?	+?

Project: Immediate breast reconstruction and radiotherapy
Appendix 4.5
Outcome variable: Overall complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients (breasts) n= (PMRT vs No RT)	Lost to follow up (n)	Length of follow up, months Mean (SD)	Results		Comments	Directness *	Study limitations *	Precision *
					Postmastectomy radiotherapy (PMRT)	No radiotherapy (No RT)				
Chetta 2017 USA	Case series	2875	0	15	Any complication 44%,		Insurance claims based retrospective case series			

ADM = Acellular dermal matrix
NR = not reported
PI = Permanent implant
RT = Radiotherapy
TE = Tissue expander

Project: Immediate breast reconstruction and radiotherapy
Appendix 5
Ethical aspects

The effect of the intervention on health	
Q1: Health: How does the intervention effect patients' health in terms of quality of life and life-length (including adverse effects)?	Post-mastectomy radiotherapy (PMRT) in implant-based immediate breast reconstructions (IBR), compared with no RT, leads to a decrease in health-related quality of life (HRQoL). Moreover, the rates of implant and tissue expander loss, re-operations and capsular contracture are significantly increased. The indication for PMRT is to avoid recurrence of the cancer and can be said to have a generally stronger medical indication than the IBR. However, given there is no knowledge on which patients having received an IBR that will receive PMRT, beforehand, and this report does not evaluate the difference between immediate and delayed breast reconstruction (DBR) – this information is difficult to use to change surgical procedures. This calls for a broader ethical analysis.
Q2: Knowledge gaps: If there is lack of scientific evidence for the effect of the intervention, are there ethical and/or methodological problems with future research in order to strengthen this evidence.	Patients cannot be randomised to PMRT or no RT as tumour factors determines whether PMRT is given or not. PMRT has to be given if it is oncologically warranted.
Q3: Degree of severity: What degree of severity has the condition the intervention is supposed to treat?	The severity of a potentially recurrent cancer is essentially the severity of breast cancer, somewhat downgraded by the risk of recurrence. Generally, this implies a high severity, also implying a higher acceptance for risks and complications, if lacking alternatives. The only alternative to reduce risks and complications in the short term, would be to abstain from an IBR before PMRT – however, assessing the ethical acceptability of this goes beyond this report.
Q4: Third parties: How does the intervention affect the health of third parties?	No direct effect on the health of third parties (see Q9 for indirect effects).
Summary: How is the benefit/risk – ration for the intervention (given the answers of Q1-Q4)?	Given the severity of a potentially recurrent cancer, the risks and complications of PMRT when having done an IBR does not seem unreasonable. Whether we would have reason to generally abstain from IBR in this group, goes beyond the scope of this analysis.
The compatibility of the intervention with ethical values	
Q5: Equality and justice: Is there a risk that access to the intervention violates the Human Dignity principle or the Swedish Discrimination Act?	It is difficult to see that access to PMRT (after having received an IBR) would violate considerations of equality and justice.
Q6: Autonomy: Can the intervention affect patients' and significant others participation in decisions and their ability to make informed and relevant decisions about the intervention?	Informed consent, requires that the patient is informed about effects, risks and complications of PMRT after an IBR. Hence, this calls for careful information processes in this case.

Project: Immediate breast reconstruction and radiotherapy
Appendix 5
Ethical aspects

Q7: Privacy: How does the intervention affect patient's and significant others' physical and personal privacy?	PMRT that results in re-operations implies a considerable intervention into the physical integrity of the patient. However, given the patient has received an IBR and wants to avoid recurrent cancer – this seems unavoidable.
Q8: Cost effectiveness: Is the balance between the cost and effects of the intervention reasonable?	The project has not presented any cost-effectiveness data, but generally, an intervention that leads to a high level of complications and might require re-operation is obviously less cost-effective. Still, since the severity of the condition is high, this might still be acceptable.
Summary: Is the use of the intervention compatible with ethical values (given the answers of Q5-Q8)?	PMRT does not seem to pose a challenge to ethical values, once that patient has undergone an IBR.
Structural factors that can affect the use and consequences of the intervention	
Q9: Resources and organisation: Are there resource- or organisational limitations that can affect who will get access to the intervention or that can lead to less access to other care if the intervention is used?	Not applicable.
Q10: Professional values: Can values within the affected care professions influence the use of the intervention and thereby lead to unequal access?	In this situation, there is no professional conflict over whether a patient should receive a PMRT or not – if they have received an IBR. There is however a professional conflict about how data on IBR in relation to PMRT should be presented. The frequency of breast reconstruction in conjunction with mastectomy is considered a quality indicator in the Swedish health care system. However, the number of reconstructive failures and patients' HRQoL are not taken into account, merely the quota of reconstructions performed. This might give a biased picture of the situation.
Q11: Stake holder interests: Are there stake holder interests that can influence the use of the intervention and thereby lead to unequal access?	It is difficult to see that any stakeholder groups would try to affect the use of PMRT in a direction, conflicting with what is medically indicated.
Summary: Are there reason to believe that an equal access to the intervention (or other care interventions) can be affected (given the answers to Q9-Q11)?	Even if PMRT in some cases will lead to risks of displacing other patients, due to acute complications, these displacements do not seem unwarranted or unavoidable – unless changing the policy on IBR in patient having undergone mastectomy – which is beyond this analysis to consider.
Long-term ethical consequences	
Q12: Long-term consequences: Can the use of the intervention result in more long-term consequences?	It is difficult to see that the use of PMRT will have any long-term ethical consequences – even in the patient group having received an IBR.

Project: Immediate breast reconstruction and radiotherapy
Appendix 5
Ethical aspects

Overall summary	
How can the ethical aspects regarding the intervention be summarised? Does this summary indicate that the intervention should be modified or that there should be special requirements associated with offering the intervention?	PMRT is medically indicated also in the group having undergone IBR, and increased risks and complications, still results in a positive balance between benefits and risks. However, the fact that PMRT for patients having undergone IBR, will result for a group of patients in loss of HRQoL, and potential complications – should be part of the information given to patients. It is important to be observant on patient not making irrational choices as a result of this information. The extra resource use resulting from acute complications, requiring surgical interventions, might result in displacement of other care – however, this seems unavoidable and acceptable if it is accepted that patient should undergo an IBR. The question whether patient should undergo an IBR or not is beyond this analysis to take a stand on.

Appendix 6
Registered studies in Clinical Trials

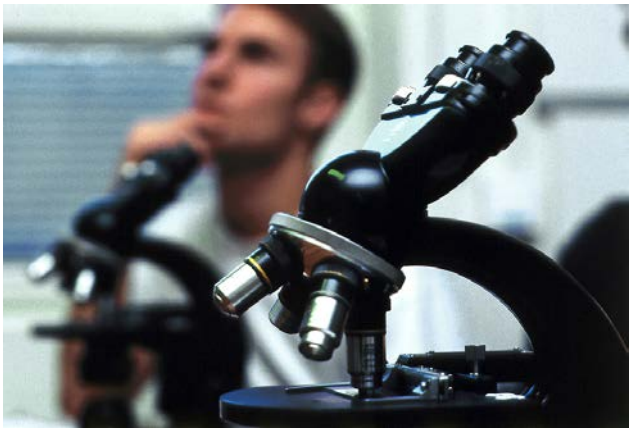
NCT Number	Main scope	Status	Conditions	Study design	URL
NCT 03730922	Delayed-immediate vs delayed IBR and RT	Not yet recruiting	Breast neoplasms	RTC	https://ClinicalTrials.gov/show/NCT03730922
NCT 01208974	NAC-sparing mastectomy and NAC RT vs skin sparing mastectomy and no RT	Recruiting	Breast Cancer, DCIS	Cohort with control group	https://ClinicalTrials.gov/show/NCT01208974
NCT 01664091	RT in delayed-immediate breast reconstruction	Active, not recruiting	Breast Cancer	Cohort	https://ClinicalTrials.gov/show/NCT01664091
NCT 03743324	Timing of RT	Not yet recruiting	Breast Cancer	Cohort with control group	https://ClinicalTrials.gov/show/NCT03743324
NCT 03627988	RT in IBR with or without CT	Not yet recruiting	Breast Cancer Invasive	Cohort	https://ClinicalTrials.gov/show/NCT03627988
NCT 02679040	Histological response of CT and RT (complications and quality of life subanalyses)	Recruiting	Breast Cancer	Cohort	https://ClinicalTrials.gov/show/NCT02679040
NCT 03101683	Chest wall RT in IBR	Not yet recruiting	Breast Cancer	Cohort	https://ClinicalTrials.gov/show/NCT03101683
NCT 03422003	Hypofractionation (short-course) RT vs conventional RT	Recruiting	Breast Cancer	RCT	https://ClinicalTrials.gov/show/NCT03422003
NCT 02608593	ADM (Strattice) vs no ADM	Unknown status	Breast Neoplasms	Cohort with control group	https://ClinicalTrials.gov/show/NCT02608593
NCT 02206477	Dimethyl sulfoxide vs no dimethyl sulfoxide in IBR with ADM and RT	Unknown status	Breast neoplasms	RTC	https://ClinicalTrials.gov/show/NCT02206477
NCT 02831426	Synthetic (TiLOOOP®) mesh vs ADM (CELLIS®) in prepectoral IBR with lipofilling (subgroup analysis for RT)	Not yet recruiting	Breast Cancer	RTC	https://ClinicalTrials.gov/show/NCT02831426

NCT 02830685	Synthetic (TiLOOOP®) mesh vs ADM (CELLIS®) in prepectoral IBR with lipofilling (subgroup analysis for RT)	Not yet recruiting	Breast Cancer	RTC	https://ClinicalTrials.gov/show/NCT02830685
NCT 03414970	Hypofractionation (short-course) RT vs conventional RT	Recruiting	Breast cancer, invasive and in situ	RTC	https://ClinicalTrials.gov/show/NCT03414970

ADM = acellular dermal matrix
CT= chemotherapy
IBR = immediate breast reconstruction
NAC = nipple areola complex
RCT = randomized controlled trial
RT = radiotherapy

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

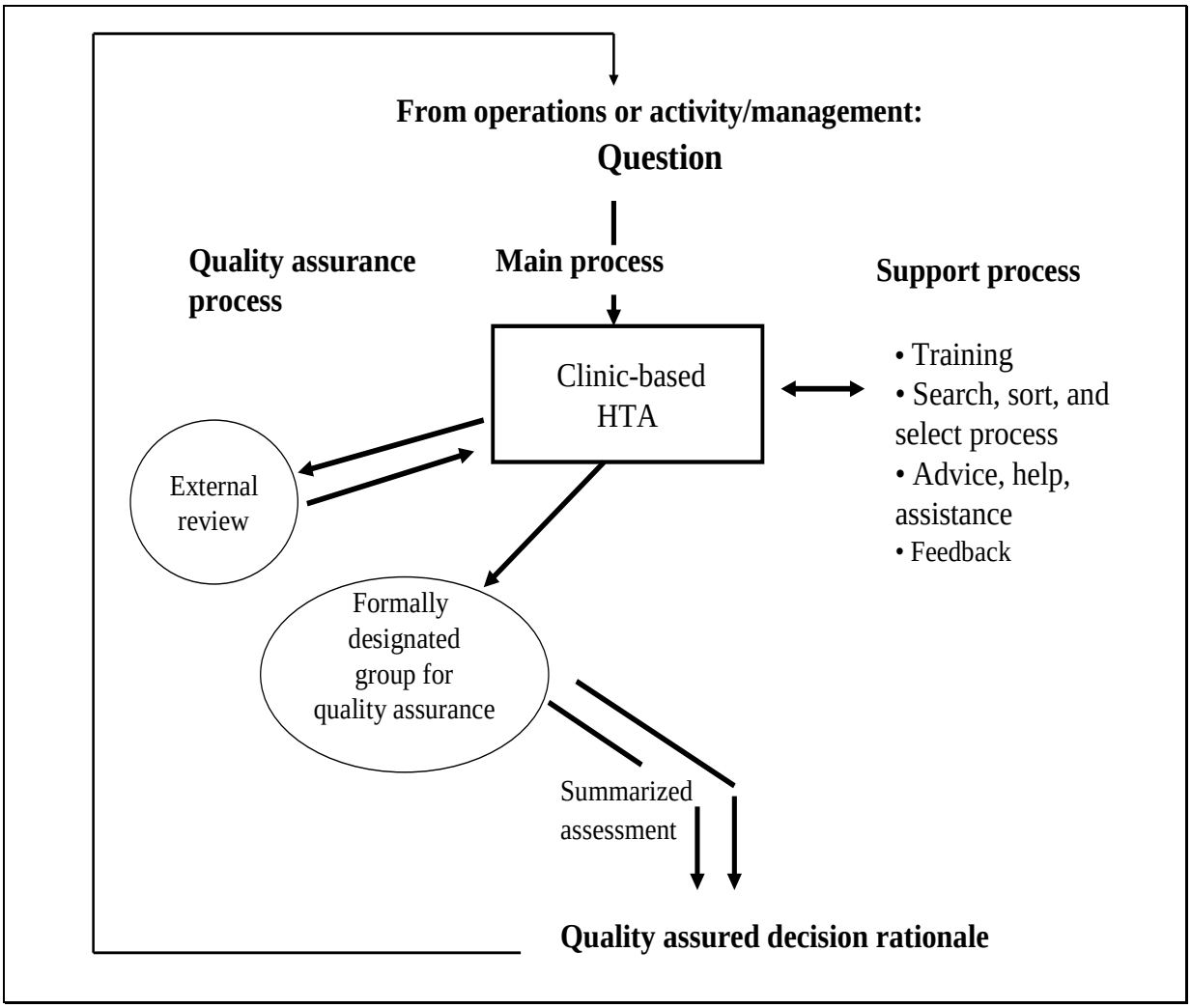
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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