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REVIEW ARTICLE

Reduction mammoplasty and mastopexy in the previously irradiated breast – a systematic review and meta-analysis

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ABSTRACT

Breast cancer is the most common cancer diagnosed in women, and early stages are treated with lumpectomy and irradiation. Irradiation, however, leads to reduced vascularization and fibrosis, which may influence the cosmetic outcome unfavourably and increase complications after subsequent surgery on irradiated breasts. Patients with significant asymmetry after treatment may desire corrective reduction mammoplasty or mastopexy, but this may be associated with increased complication rates. This systematic review and meta-analysis aimed to investigate postoperative complication rates after bilateral reduction mammoplasty or mastopexy in women who had undergone unilateral lumpectomy and irradiation. PubMed, Medline, EMBASE and Cochrane databases were searched for eligible studies. After screening titles and abstracts, 14 full text studies were reviewed, and 7 of these were included in the analysis. The meta-analysis showed a significantly higher complication rate in the irradiated breast compared to the non-irradiated breast, rate ratio 4.82 (95% CI: 1.58, 14.70), $p = 0.006$. The complication rate was 54% in the irradiated breast (58/107) compared to 8% (9/107) in the non-irradiated breast ($p = 0.034$). This study suggests that reduction mammoplasty or mastopexy in the previously irradiated breast is associated with a significantly increased risk of complications. Careful patient selection and information are paramount in the treatment of this patient group.

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Irradiation; radiation; reduction mammoplasty; mastopexy; complication; breast surgery

1. Introduction

Breast cancer is the most common cancer diagnosed in women, and is the second leading cause of female cancer mortality in the Nordic countries [1]. Screening programs and improved technology for early detection ensures that more patients are diagnosed in early stages. Breast conservation therapy (BCT) for breast cancer entails lumpectomy followed by total breast irradiation, and is currently the recommended treatment for early stage breast cancer [2,3].

Radiation, however, causes tissue ischemia and cellular alterations leading to wound healing problems and fibrosis [4,5]. Due to this, radiotherapy is generally considered a contraindication to aesthetic surgery of the breast. In addition, significant asymmetry may follow after BCT [6,7] along with poor cosmetic results [8]. This is particularly true for macromastia patients, as inferior cosmetic results have been reported in this patient group [9]. This may be due to the increased breast volume exposed to radiation, a higher amount of energy used to deliver the prescribed dose, and thus higher risk of complications.

Reduction mammoplasty is the gold standard for treating macromastia and breast asymmetry, as the procedure significantly reduces physical and psychological symptoms associated with the condition, and increases quality of life [10,11]. As with any surgical procedure, complications may arise. Smoking, increased body mass index (BMI), increasing resection weight and higher age are correlated with an increased risk of complications after reduction mammoplasty in non-irradiated breasts [12–14].

Implant-based and autologous breast reconstruction in the previously irradiated breast is known to be associated with an increased complication rate [15,16]. However, little is known about the risk of complications after reduction mammoplasty in previously irradiated breasts. In 1992, Handel et al. [17] published a case report demonstrating prolonged wound healing, edema, nipple necrosis and partial loss of the areola in the irradiated breast after reduction mammoplasty. Two later case reports reported uneventful healing in four patients undergoing bilateral reduction mammoplasty after unilateral breast irradiation, except for prolonged edema in one patient [18,19]. Conflicting results have since been published, and surgeons have been cautious in performing breast reductions in the previously irradiated breast. A study showed that irradiated breasts had a significantly increased risk of postoperative infections after reduction mammoplasty compared with non-irradiated breasts [20].

The objective of this systematic review is to investigate if complication rates are higher in the previously irradiated breast compared to the non-irradiated breast, in women undergoing bilateral breast reduction mammoplasty after unilateral BCT and irradiation for breast cancer.

2. Materials and methods

2.1. Search strategy and selection criteria

This systematic review was conducted according to the guidelines recommended by the Preferred Reporting Items for Systematic

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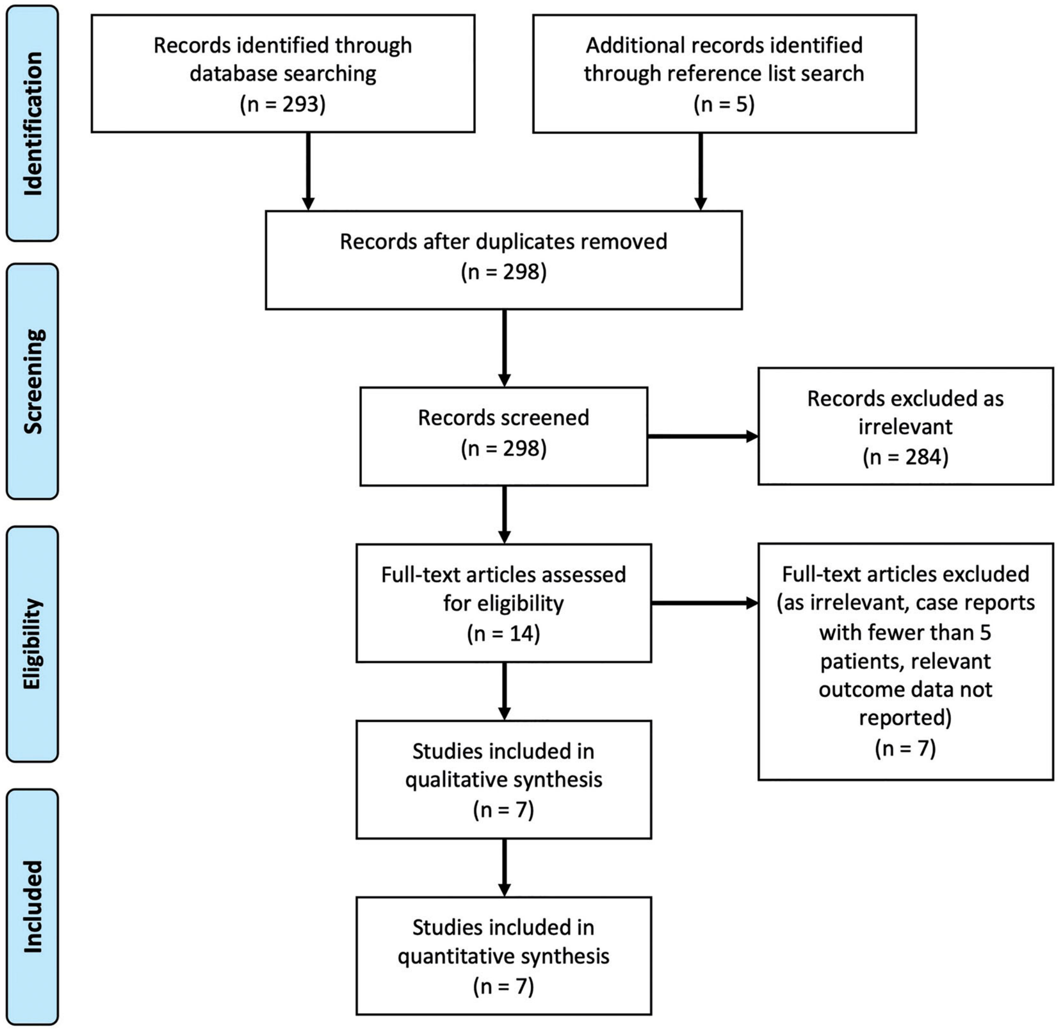

Figure 1. Flow diagram on study selection.

Review and Meta-Analysis (PRISMA) [21]. No review protocol was registered for this study. Eligibility criteria for inclusion were: all published studies, including cohort, case–control, retrospective and case studies investigating or providing information about complications after reduction mammoplasty or mastopexy on a previously irradiated breast. We excluded reviews, animal studies, letters to editor, small case studies with less than five patients due higher risk of publication bias in smaller studies [22,23], and studies not reporting postoperative complications separately for irradiated and non-irradiated breasts. We did not apply restrictions regarding language, study date or operative technique. We searched PubMed, Medline, EMBASE and Cochrane databases for eligible studies using the following key words in the title: 'radiation', 'breast irradiation', 'irradiated' or 'radiated', and 'reduction mammoplasty', 'reduction mammaplasty', 'mastopexy', or 'breast surgery'. In addition, reference lists of included studies and relevant review articles were hand-searched. The resultant 298 titles were screened for eligibility. After removal of irrelevant titles, 19 abstracts were screened, yielding 14 studies for full-text review. Seven studies met the eligibility criteria and were included in this review. All studies were screened by AKL and LH, and in cases of disagreement the studies were discussed in the entire author group until consensus on inclusion or exclusion was reached. Figure 1 illustrates the study selection process. The search was performed on the 31 January 2019.

2.2. Data extraction

Outcomes were type and frequency of postoperative complications in the irradiated vs. the non-irradiated breast, defined as any postoperative condition defined as a complication by the study authors. There was a large degree of heterogenicity regarding the classification of complications as major or minor, and many studies made no such division. Here, we define major complications as those requiring or presumed to require treatment (medical or surgical), and minor complications as those that did not require further intervention. In addition, data regarding study design, year of publication, number of patients included, and study location was extracted. We also extracted demographic and clinical data on the study population (age, BMI, smoking status, comorbidities, breast cancer stage), as well as details on the treatment received (radiation dose, reduction mammoplasty or mastopexy, surgical technique, duration between radiation therapy and surgery, chemotherapy treatment, prophylactic antibiotics, average specimen weight). For studies in which additional data was required, we contacted study authors for further information.

2.3. Data analysis

Complications were reported as events, so multiple events could potentially be reported for each patient. Therefore, outcomes were treated as count data and results from studies calculated as

Table 1. Characteristics of included studies.

	N	Study period	Mean Age (range)	Mean BMI	Smoking	Comorbidities	Radiation dose	Mean time from irradiation to operation	Specimen weight IB	Specimen weight NIB	Surgical technique
Weichman et al. (2015) [43]	13	2001–2013	50 years (33–64)	27	6 former	3 hypertension 2 hypothyreoidism 2 asthma 1 diabetes	60 Gy	41 months	254 g	387 g	Central Mound
Spear et al. (2014)[a] [30]	18	1995–2012	50 years (35–69)	29	1 former	–	–	30 months	623 g[b]	–	Reductions: inferior, medial, central mound, superomedial, superolateral, and McKissock. Mastopexies: circumvertical, inferior wedge excision, and free nipple graft techniques
Dal Cin et al. (2012) [26]	9	1980–2007	56 years	30	–	3 hypertension 1 rheumatoid arthritis	50 Gy	65 months	490 g	664 g	Inferior pedicle (superior pedicle in one patient)
Munhoz et al. (2011) [31]	38	1999–2009	52 years (39–66)	25	8	4 hypertension 2 diabetes	45–50 Gy[c]	22 months	–	–	Superior-medial 17 (44.7%), superior 13 (34%), inferior 6 (16%), superior-lateral 2 (5%)
Parrett et al. (2010) [32]	12	2004–2008	57 years (47–64)	30	0	2 diabetes	55 Gy	86 months	306 g	599 g	2 Wise pattern, 3 SPAIR, 7 Robertson
Chin et al. (2009)[a,d,e] [33]	7	1997–2007	49 years	33	0	1 hypertension	60 Gy	78 months	892g		Reductions: Wise-pattern pedicle ($n = 5$), breast amputation with free nipple graft ($n = 2$)
	6		48 years	32	0	2 hypertension	62 Gy	52 months	230 g		Mastopexies: Vertical or T-shaped technique
Christiansen et al. (2008) [34]	5	2001–2005	50 years (41–56)	–	–	–	–	67 months	291 g	533 g	Omega pattern in irradiated breast, inferior pedicle central mound in non-irradiated breast
Total/mean	107		52	29			56 Gy	55 months	386 g	411 g	

[a]Study includes data from both breast reductions and mastopexies.
[b]Breast reductions only.
[c]Including a 10 Gy boost to the tumor site.
[d]Data given for breast reductions (top line) and mastopexies (lower line).
[e]One reduction mammoplasty patient had an additional mastopexy performed due to undercorrected asymmetry.
'–' indicates that the data was not reported in the study.

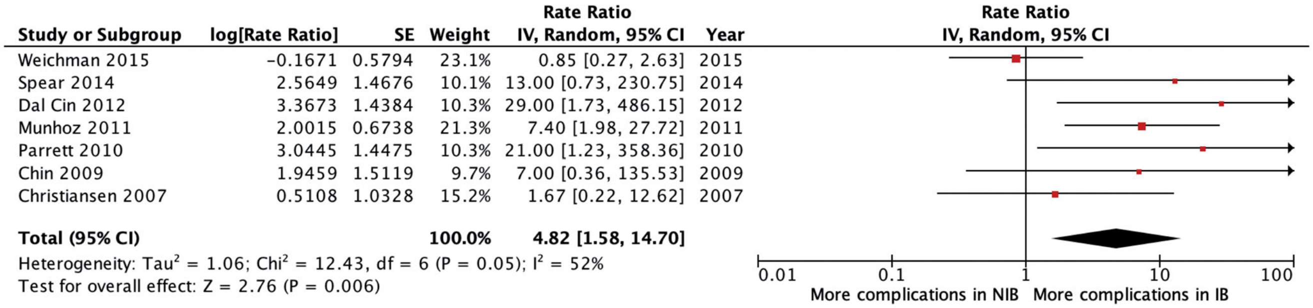

Figure 2. Forest plot depicting the meta-analysis of total complication rates in the included studies.

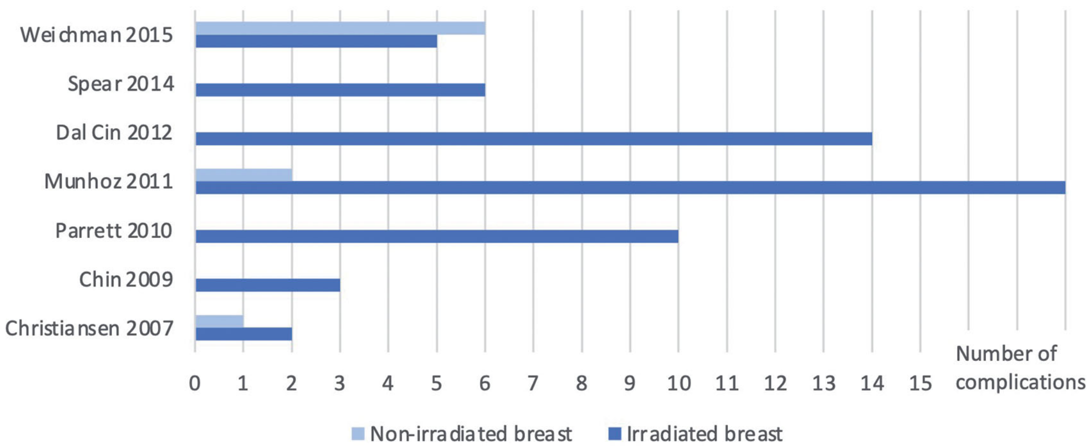

Figure 3. Number of complications seen in the irradiated breast compared to the non-irradiated breast in the included studies.

rate ratios. Data analyses were performed using Review Manager version 5.3.5 [24].

The studies were combined by the generic inverse-variance method on the natural logarithms of rate ratios (RR) and the standard error (SE) of the rate ratio as described in the Cochrane Handbook [25]. A random-effect model was used and 0.5 was added to all counts as zero counts were present, which is not allowed in the model.

For analysing individual complication results from different studies, results were analysed using a random effect Mantel–Haenszel method [25]. Effects were reported using risk differences (RD) and were given with 95% confidence intervals (CIs) for complications. Analyses were made for complications reported by four or more studies. One study reported data on 'infection' and 'second infection', these data were pooled in the analysis [26].

To evaluate if there was a significant difference in the number of studies reporting more complications in irradiated breasts compared to non-irradiated breasts, we performed a Wilcoxon-signed-rank test.

2.3. Quality and GRADE assessment

We used the Newcastle-Ottowa Scale (NOS) for assessing the quality of non-randomized studies [27]. We used the GRADE approach to determine the quality of the evidence and strength of recommendations [28,29].

3. Results

3.1. Characteristics of included studies

The characteristics of the seven included studies are shown in Table 1. All were retrospective studies that collected data *via* a retrospective review of medical records. Patient cohorts were small, with between five and 38 patients included. Mean age was 48 to 57 years, and mean BMI was between 25 and 33 kg/m^2. Only one study included active smokers, some did not report smoking status, while the remaining had only performed surgery on former or non-smokers. In the majority of studies, a small fraction of patients suffered from comorbidities such as hypertension, diabetes and asthma, however, the population included was not a heavily comorbid one (Table 1). Radiation doses ranged from 45 Gy to 62 Gy, given on average 22–86 months prior to reduction mammoplasty or mastopexy. An average of 230 g−892 g had been resected in the previously irradiated breast, compared to 387 g−664 g in the non-irradiated breast. Mean follow up ranged from 10 to 47 months. A variety of surgical techniques were used, including the central mound technique, Wise pattern, The Short Scar Periareolar Inferior Pedicle Reduction (SPAIR), Robertson and omega pattern technique for reduction mammoplasties, and circumvertical, inferior wedge excision, and free nipple graft techniques for mastopexies (Table 1).

All included studies investigated postoperative complication rates for the irradiated vs. the non-irradiated breast after bilateral reduction mammoplasty or mastopexy in women who had undergone unilateral lumpectomy and irradiation [24,26,30–34].

However, Munhoz et al. [31] at the University of São Paolo School of Medicine in Brazil investigated 144 patients who underwent BCS with immediate (before radiation therapy) or delayed (months to years after radiation therapy) bilateral reduction mammoplasty or mastopexy between 1999 and 2009 in order to determine if immediate or delayed surgery entailed higher complication rates. Only data from the 38 patients who underwent delayed surgery and received irradiation therapy after BCS, are included in the current study and given here. Median

Table 2. Complication rates reported in the included studies, reported as major and minor complications.

Authors	N	Major complications										Minor complications								Total	
		Nipple-Areola necrosis		Fat Necrosis		Skin Necrosis		Infection		Hematoma		Wound Healing Problems		Hypertrophic Scar		Seroma		Edema			
		IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB	IB	NIB
Weichman et al. (2015) [43]	13	0	0	1	1	–	–	2	0	0	1	1	1	1	3	–	–	–	–	5	6
Spear et al. (2014) [30]	18	–	–	1	0	1	0	1	0	–	–	3	0	–	–	–	–	–	–	6	0
Dal Cin et al. (2012) [26]	9	1	0	–	–	–	–	8	0	–	–	2	0	3	0	–	–	–	–	14	0
Munhoz et al. (2011) [31]	38	1	0	4	0	7	1	2	0	–	–	4	1	–	–	–	–	–	–	18	2
Parrett et al. (2010) [32]	12	0	0	2	0	–	–	2	0	–	–	1	0	–	–	5	0	–	–	8	0
Chin et al. (2009) [33]	12	–	–	–	–	–	–	–	–	–	–	1	0	1	0	–	–	1	0	3	0
Christiansen et al. (2008) [34]	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	2	1
Total	107	2	0	8	1	8	1	15	0	0	1	12	2	5	3	5	0	3	1	58	9

IB: irradiated breast; NIB: non-irradiated breast. '–' complication not reported.

specimen weight was 142 g, however, it is not noted if this is the median for both irradiated and non-irradiated breasts or only one of the groups.

Spear et al. [30] at Georgetown University Hospital in Washington, DC, USA, performed a retrospective review on 12 patients undergoing reduction mammoplasty and six undergoing mastopexy after BCT and irradiation. The study does not mention the complication rates for non-irradiated breasts. We contacted the study authors, who informed that no complications were seen in the non-irradiated breasts. This was used in our analysis. One patient experienced a major complication with loss of the nipple and 50% of the breast tissue, requiring reconstruction with a latissimus dorsi musculocutaneous flap.

Chin et al. [33] at the Baystate Medical Center in Springfield, USA, investigated seven patients undergoing breast reduction, and six patients undergoing mastopexy after unilateral BCT and irradiation. One reduction mammoplasty patient had an additional mastopexy performed due to undercorrected asymmetry.

3.2. Postoperative complications in the irradiated and non-irradiated breast

A total of 58 complications occurred in 107 irradiated breasts (54%), and 9 complications in 107 nonirradiated breasts (8%). The meta-analysis showed a significantly higher complication rate in the irradiated breast than the non-irradiated breast, RR: 4.82 (95% CI: 1.58, 14.70), $p = 0.006$ (Figure 2). Six studies reported more complications in irradiated breasts ranging from 1 to 16 and one study reported one more complication in the non-irradiated breasts, $p = 0.034$ Wilcoxon-signed rank test. The mean numbers of reported occurrences were 8.3 and 1.3, respectively (Figure 3).

Complications comprised wound healing problems, nipple-areola necrosis, infection, fat necrosis, hematoma, hypertrophic scarring, skin necrosis, seroma and edema. Complications were divided into major complications (nipple-areola necrosis, fat necrosis, skin necrosis, infection and haematoma) and minor complications (wound healing problems, hypertrophic scarring, seroma and edema). There were a total of 58 complications in irradiated breasts and 9 in non-irradiated breasts. 36 of these were considered major and 31 minor (Table 2).

3.3. Quality and GRADE assessment

As can be seen from Table 3, the studies all scored rather high on the Newcastle Ottowa Quality Assessment Scale. The study cohorts exclusively included women who served as their own control, since one breast was non-irradiated and healthy, while the other breast was irradiated after BCT. In this setting, all possible confounders are balanced between the control group and intervention group, making adjustments unnecessary. This a major factor for the good NOS scores. However, all the included studies presumably suffered from selection bias, since the cohorts are very small, and data often gathered over many years (Table 1), which indicates that only selected patients were operated. None of the studies contain information about the number of women evaluated and how many were turned down for surgery or offered operation, which makes it difficult to estimate the generalizability of the results. All outcomes were identified from medical records, however, only few studies predefined outcomes (for instance predefining infection as an infection requiring intravenous antibiotics), which makes comparisons very difficult.

Table 3. The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies.

Study (publication year)	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Total (max 9 stars)
Weichman et al. (2015) [43]	***	**	***	8
Spear et al. (2014) [30]	***	*	**	6
Dal Cin et al. (2012) [26]	***	**	***	8
Munhoz et al. (2011) [31]	***	**	***	8
Parrett et al. (2010) [32]	***	**	***	8
Chin et al. (2009) [33]	***	**	***	8
Christiansen et al. (2008) [34]	**	**	*	5

3.3.1. GRADE assessment

As all studies are non-randomised, the quality rating *a priori* starts at low quality of evidence. As all studies have few patients and few events, all studies were downgraded due to imprecision. Therefore, the quality of evidence is very low.

4. Discussion

In this systematic review and meta-analysis, we present summary data from all eligible studies on complications after reduction mammoplasty or mastopexy in the previously irradiated breast. Our meta-analysis shows a significantly increased overall complication rate of 4.82 (CI: 1.58–14.70, $p = 0.006$) in irradiated breasts compared to non-irradiated breasts.

In addition, a complication rate of 54% was found in the irradiated group, compared to a rate of 8% in the non-irradiated group. This suggests that surgery on a previously irradiated breast is associated with a very high risk of complications. The acute reaction to radiotherapy is inflammation that over time may lead to fibrosis with manifestations including tissue atrophy, necrosis, vascular damage and chronic ulceration in the tissue [35]. This usually develops within 4–12 months after radiotherapy and can progress over several years [36]. The radiation induced fibrosis is chronic and does not resolve. Tissue damage includes chromosomal alteration, inhibition of fibroblast action, and occlusion of microvasculature, resulting in regional ischemia [15]. The cellular structure of the skin changes, and damage to skin appendages occur. Acute radiation effects include erythema, tenderness, desquamation, hyperpigmentation and ulceration, while late radiation injury includes tissue atrophy, necrosis, vascular damage and chronic ulceration, ultimately leading to fibrosis [5].

In the included studies, details of radiation dose and fractionation or boost to the tumor bed is not described. The doses given are within the standard range used for breast irradiation after breast conserving surgery. The risk of severe or moderate fibrosis is increased when a radiation boost is given to the tumor bed and with larger breasts [37]. The grade of fibrosis or other side effects to radiotherapy are not described in the included studies. Again, this may reflect a selection bias in these studies, as surgeons would be reluctant to operate on breasts with severe fibrosis.

The risk of complications after breast cancer surgery must always be carefully considered and minimized as much as possible. Complications such as infection, hematoma, seroma, necrosis or delayed wound healing, even of the contralateral breast if this also has been operated, can postpone adjuvant chemotherapy and/or radiotherapy. Radiotherapy should be given no later than 12 weeks after breast conserving surgery for breast cancer [38], or no longer than 7 months after surgery if given sequentially after chemotherapy [39]. Data from a Danish nationwide study showed no difference in time from surgery to onset of chemotherapy in patients treated with either mastectomy, breast conserving surgery or oncoplastic surgery [40], suggesting patients should not be excluded from oncoplastic surgery before adjuvant oncological treatment. However, in this study a selection bias cannot be excluded, since patients with serious comorbidity may not have had the same offer of for instance an oncoplastic procedure as more healthy individuals.

In addition to timing, other factors may influence the complication rate. In the included studies, many different operative techniques have been used by many different surgeons. The heterogeneity and small number of studies, which all had very low quality, did now allow for further investigation of which surgical techniques provided superior results. This is a significant limitation to the study. However, in general, a broader pedicle is recommended when possible as it ensures better vascularization for the nipple-areola complex. In non-irradiated breasts, the superior pedicle has shown results equal to the inferior pedicle [41]. Kronowitz et al. [42] investigated different surgical techniques in the irradiated breast, and found that the superior pedicle was associated with increased complication rates. Weichman et al. [43] used the central mound technique, which may be more reliable than the inferior pedicle. However, obtaining satisfactory cosmetic results for large breasts with this technique may prove more challenging. Reduction mammoplasty with a free nipple graft is considered a good alternative to a pedicled reduction technique with a lower risk of NAC necrosis, since no pedicle is needed.

Only four studies reported the average resected volume in the irradiated breast compared to the non-irradiated breast (Table 1). In these studies, it is evident that a larger volume of tissue was removed from the non-irradiated breast, presumably due to the prior lumpectomy and post-radiation shrinkage in the BCT-treated breast. Reducing the volume of tissue resection may be crucial in reducing postoperative complications in the irradiated breast, but the limited data available does not provide evidence for any conclusions in this regard.

As each woman served as her own control, all possible confounding factors were balanced between the irradiated and the non-irradiated group. Therefore, it was not possible to analyze the significance of BMI, smoking status and comorbidities on the complication rates in this meta-analysis. However, increased BMI has been identified as a risk factor for developing complications after breast reductions without irradiation [20,44], and comorbidity such as diabetes has also been shown to increase postoperative complication rates [45].

Fat necrosis is the most dreaded complication in the irradiated breast, and if severe, can lead to large volume deficiencies. Salvage procedures may be required, as in the study by Spear et al. [30]. In cases of significant volume deficiencies, partial breast reconstruction with importation of tissue in the form of local fascio-cutaneous perforator flaps [46], musculocutaneous flaps [47]; or even free flaps can be used [48], in addition to autologous fat grafting [49].

Attempts at reducing postoperative complications by using prophylactic measures have been described. Snyder et al. [50]

reported data on five patients treated with reduction mammoplasty on previously irradiated breasts, combined with adjuvant hyperbaric oxygen therapy pre- and postoperatively. Delayed wound healing was reported in two irradiated and two non-irradiated breasts, but no further complications were seen. Hyperbaric oxygen therapy increases angiogenesis and vascularization and may prove beneficial in reducing postoperative complications. However, the feasibility of this protocol limits its clinical use, and evidence for this preventive measure is lacking. In another case report, Sterodimas et al. [51] used buflomedil (a vasoactive agent that increases microcirculation) in a patient undergoing bilateral breast reduction after unilateral lumpectomy and irradiation. Buflomedil was administered intravenously for 2 days, followed by a 14-day oral course. No complications were seen. With only one study investigating the benefit of buflomedil in reducing postoperative complications, further studies are needed.

Postoperative infections can be countered using perioperative antibiotics. However, prolonged prophylactic treatment with antibiotics is not recommended due to issues regarding resistance and lack of evidence of effect.

After the conclusion of our literature search, a French literature review examining outcomes after reduction mammaplasties on irradiated breasts was published [52]. In line with our investigation, the study finds increased complication rates in irradiated breasts.

As complication rates are higher in irradiated breasts, some authors have investigated if immediate breast reduction is preferable to delayed reduction mammoplasty [53]. Indeed, Munhoz et al. [31] found increased complication rates in patients undergoing delayed breast reduction. Oncoplastic breast surgery (OBS), in which breast reduction or reconstruction is performed at the time of lumpectomy and thus prior to irradiation, has been shown to allow for wider excisions and provide favorable cosmetic results [53]. In addition to improved cosmesis, OBS has proven to be oncologically safe, providing better control of tumor margins and results in high patient satisfaction [54]. However, additional procedures may be needed with time, since symmetry after immediate reduction or mastopexy in the healthy breast may not be long-lasting. The need for performing post-irradiation reduction mammoplasties could be minimized by the widespread use of OBS. The involvement of plastic surgeons in multidisciplinary teams treating breast cancer would allow for a more widespread use of OBS, which may be the treatment of choice in many countries. However, in Scandinavia OBS as discussed in this paper is not offered to all eligible breast cancer patients as a standard of care. If reduction mammoplasty after irradiation and BCT indeed does lead to increased complication rates, one may argue that OBS should be more widely offered to eligible patients.

Though all published records were screened, only seven studies were included. Although the majority of studies were performed at large university hospitals including patients over many years, patient cohorts are generally small. The scarcity of data likely illustrates that most surgeons consider prior irradiation a relative contraindication to elective breast surgery. In addition to the sparse data material, conclusions may be limited by very selected patient cohorts. As irradiated tissue is known to have poor healing potential due to reduced vascularization [55], only selected patients without significant comorbidities, obesity, significant sequelae after irradiation, or positive smoking status may have been offered surgery. No data on this selection process is available, and the grade of evidence is very low, so results must be interpreted with this in mind. The strength of recommendation is thus weak.

As only few studies have been undertaken in this area, more and higher quality research is needed to firmly establish the risk of performing surgery on irradiated breasts.

5. Conclusion

This study suggests that reduction mammoplasty or mastopexy in the previously irradiated breast is associated with a significantly increased risk of complications. Careful patient selection and information are paramount in the treatment of this patient group.

Disclosure statement

All authors declare no conflicts of interest.

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