



Short Communication

Superficial margins in skin sparing and nipple sparing mastectomies for DCIS: A margin of potential concern



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ABSTRACT

Skin-sparing and nipple-sparing mastectomies with immediate reconstruction for breast cancer are increasing. The superficial fascia is considered a natural border and the superficial margin may not be evaluated. We emphasize the need for reporting of the superficial margin status in these procedures to obtain valid information on its association with local recurrence risks.

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Ductal carcinoma in situ (DCIS) accounts for 20% of all newly diagnosed breast neoplasias in a screened population [1]. Breast-conserving surgery with postoperative radiation therapy (RT) or mastectomy, both with/without endocrine therapy, is considered the standard of care [2]. In case of mastectomy, postmastectomy RT is rarely applied, and may be used if surgical margins are close or involved [3–5].

In the past years, the rate of skin-sparing (SSM) and nipple-sparing mastectomies (NSM) is increasing for both DCIS and invasive cancer, allowing for immediate breast reconstruction and restoration of the breast mound with either an expander, permanent implant, or autologous tissue during the primary procedure [6,7].

This surgical approach of SSM/NSM with immediate reconstruction presents, however, a dilemma between safeguarding skin flap (of the breast) viability and the quest to remove as much breast tissue as required to secure oncological safety [8,9]. The potential of leaving residual breast glandular tissue after SSM/NSM is associated with the thickness of the skin flap and location, with most residual breast tissue found under the nipple and areola complex [9,10]. This was assumed to be the reason for high ipsilateral local recurrences observed in breast cancer BRCA1/2 mutation carriers treated with SSM/NSM without PMRT compared to those with a

more advanced breast cancer stage who received PMRT [11]. As local recurrence of invasive breast cancer can result from lymphovascular invasion into the subcutaneous lymphatic plexus, beside from residual glandular tissue or residual disease, it is expected that the rate of DCIS recurrences after margin free SSM/NSM will be lower (~1% recurrence rate of DCIS after mastectomy) as compared to invasive cancer [5,11].

In the following short communication, we present three patients treated with SSM/NSM for DCIS showing residual DCIS at the superficial margin (Figs. 1 and 2). These cases illustrate the risk of a subsequent local recurrence possibly due to residual breast glandular tissue and/or disease left after NSM/SSM. In two of the cases, the patients underwent re-excision which was positive for disease, and the third patient was referred to close follow-up and had early local recurrence with invasive disease.

It is important to understand that the risk of residual glandular tissue and/or disease relies in the nature of the NSM/SSM, regardless of surgeon expertise [9,12,13]. To preserve the native breast skin, the surgeons need to separate the mammary gland from the subcutaneous fat at the level of the superficial fascia (the ventral sheet of the pectoral fascia). This fascia is described as a definite but very delicate and discontinuous structure that may be challenging to identify [13,14]. Notably, limits of anatomic extension of the fibroglandular tissue may be imprecise and show substantial variation from a very definite distinction between breast tissue and subcutis or breast glands being intertwined with skin adnexa [13]. The thickness of the subcutis is variable and distance from

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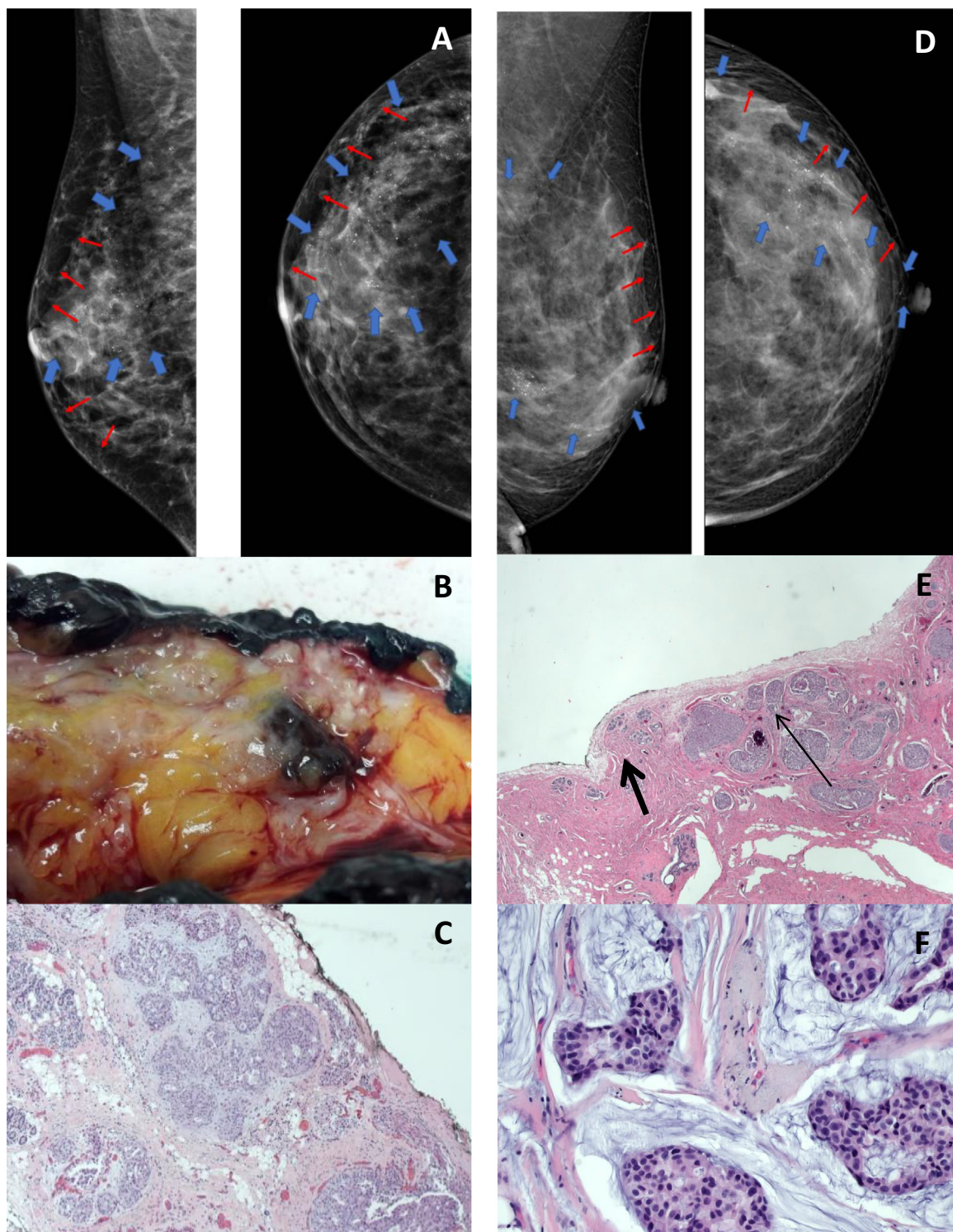


Fig. 1. A, mammography of a 31-year-old woman presenting with a palpable mass in the upper outer quadrant of the right breast. Microcalcifications with an extension of 12 cm are noted by the blue arrows and red arrows are indicating the borders of the breast tissue. Core needle biopsy showed DCIS, and the patient underwent SSM, immediate reconstruction and sentinel node biopsy. Histopathology showed DCIS, grade 2-3, without invasive carcinoma. DCIS was present within 0-0.1 mm of the superficial margin in upper outer quadrant as well as of the lateral margin (towards sector D) with abundant normal glands close to the margins. B shows breast tissue with macroscopically suspicious changes extending to the inked margin and C shows extensive DCIS close to the margin. The patient had a re-resection showing 9 mm DCIS "on the ink" in the "new" superficial resection margin associated with considerable amount of residual glandular tissue. D, a mammography showing microcalcifications with an extension of 10 cm in a 46-year-old woman presenting with a palpable mass in the lower outer quadrant of the left breast. Core needle biopsy showed DCIS, and she underwent SSM, immediate reconstruction and sentinel lymph node biopsy. Histopathology showed DCIS, grade 3, 25 mm. DCIS was focally present at less than 0.5 mm from the superficial margin in the outer quadrants. E shows abundant normal breast glands (thick arrow) and DCIS (thin arrow) close to margin. No re-resection was performed, but the patient was followed with ultrasound (US) after 6 months, MRI after 12 months, and mammography/US after 2 years and 2½ years; all without suspicious findings. The patient presented after 4 years with an invasive local recurrence towards the upper outer quadrant (F).

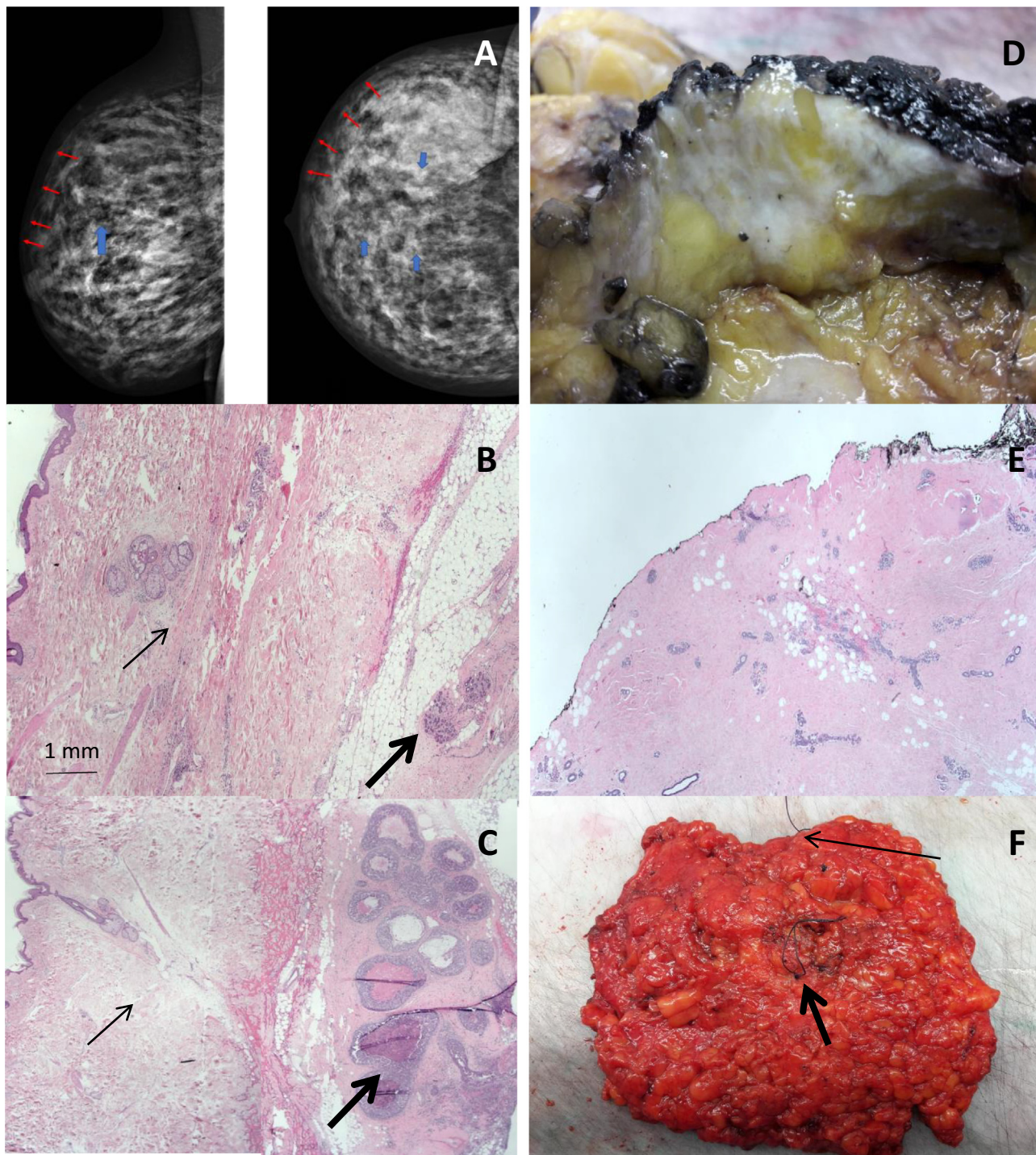


Fig. 2. A, mammography with microcalcifications extending from 11 to 3 o'clock in a 33-year-old, lactating woman, presenting with a palpable mass in the upper outer quadrant of the right breast (Blue arrows indicating microcalcifications and red arrows indicating the borders of the breast tissue). Core needle biopsy showed DCIS and a microinvasive focus of invasive ductal carcinoma (IDC). The patient underwent SSM, immediate reconstruction and sentinel lymph node biopsy. Histopathology showed 70 mm DCIS with >10 foci of IDC, grade II (tumour diameters 1–7 mm), ER+, HER2-, Ki67 30%; 1 of 3 SN had clusters of tumour cells, but no micro- or macrometastases. Invasive carcinoma was present “on the ink” and DCIS < 1 mm from the superficial margin with abundant normal glandular tissue present in the surroundings. A re-resection of skin in the upper outer quadrant was performed showing an 8 mm focus of DCIS without invasion, very close to the skin with <1 mm to the margin and with residual glandular tissue present very close to the dermis. B shows normal breast glands (thick arrow) and C a large focus of DCIS (thick arrow) separated from the dermis (thin arrows in both pictures) by a very thin layer of subcutaneous fat. The dermis is thickened due to fibrosis after previous surgery. D, E shows abundant normal breast tissue extending to the superficial inked margin in a subcutaneous mastectomy - macroscopically and microscopically, respectively. F Nipple sparing mastectomy specimen with one suture at the cranial border (thin arrow) and one suture marking the nipple base (short, fat arrow). Otherwise, no landmarks are present to determine location of a possible close margin.

superficial margin to glandular tissue may vary between 0 and 10 mm within the same breast (measurement made by pathologist), as reported in the prospective SKINI trial [9]. Additionally,

glandular tissue may be found in various amounts within the subcutis [15] and as part of Coopers ligaments. A thinner breast skin flap (<5 mm) may reduce the amount of residual glandular tissue,

but it needs expertise not to compromise an adequate blood supply and achievement of an acceptable aesthetic result [9]. Furthermore, at time of surgery, the access incision during NSM/SSM is small and offers limited overview, and the surgeon's perioperative estimation of a resection at the superficial fascia level may not be consistent with microscopic findings. As a consequence of the surgical and anatomical challenges described above, unequivocal resection within the mammary gland may, not infrequently, be verified macro- and microscopically and will as such be associated with varying amounts of residual breast tissue left in the patient (Fig. 2D,E).

Preoperative breast ultrasound (US) or preferably MR-mammography can be used to assess the thickness of the subcutaneous fat, and indocyanine green fluorescent angiography [16] may be used perioperatively to allow further removal of tissue without compromising vascularization. Furthermore, the amount of residual glandular tissue might vary by the reconstructive approach, with a tendency for leaving a thicker flap in case of pre-pectoral reconstruction compared to a retro-pectoral reconstruction. Therefore, potential more residual breast tissue will be left with the pre-pectoral reconstruction [13].

However, there are no clear guideline to indicate in which patients that these procedures can be done safely [17]. In case of DCIS, contraindications for NSM are microcalcifications close to the subareolar region, tumour < 2 cm from the nipple, Paget's disease of the nipple and/or nipple discharge [2,18], but not much data exists regarding the maximum extent of disease in which these procedures can securely be performed [17]. Notably, DCIS is, however, more often associated with clinically inapparent disease and skip lesions away from the primary lesion than invasive ductal carcinoma [19]. Even if preoperative breast MRI is used, estimating the extent of disease may be challenging [20], which may be further accentuated by the histological nature of DCIS [19].

Few studies indicate the rate of residual disease after these procedures. A study of 64 SSM cases (for DCIS and invasive cancer) showed involvement of the superficial margin in 38% and removal of an additional superficial margin directly over the tumour resulting in 13% involved superficial specimen margins, mostly in the presence of extensive DCIS. In 53% of superficial margins, residual glandular tissue was found [21]. In another study, including 1147 patients, the re-excision rate due to close/positive margins in SSM/NSM (for DCIS or invasive cancer) were reported to be higher than for simple mastectomy (19.8 vs. 9.3%, $p < 0.001$) [22]. However, only a limited number of retrospective studies reported on local or locoregional recurrences after these procedures, showing conflicting results, ranging between 1% and 6% recurrences [22–25]. Other studies have shown a higher local recurrence associated with high-grade disease and margins less than 1 mm [4,26,27]. Nevertheless, these studies do not clearly indicate the use of postoperative treatment or RT. Disturbingly, younger patients (<40 years) tend to undergo more often SSM with immediate reconstruction, but are also associated with a higher locoregional rate after mastectomy for DCIS, irrespective of the procedure [24,28,29]. Timbrell et al. [24], indicated that clear margins are needed in case of SSM for pure DCIS to reduce the rates of recurrences, and recommended to consider re-excision (including overlying skin) particularly in young women with high-grade and ER-negative DCIS.

Our report raises an important issue for DCIS and for invasive breast cancer. As the superficial fascia is considered a natural border and only the nipple base in NSM is considered a true resection margin, the superficial margin may not be evaluated or reported. In DCIS, margins may be assumed to be clear, since subcutis/skin are not likely to be involved due to the non-invasive nature of the lesion and because of the extent of the surgical procedure [5]. However, Clements et al. [5], reported that up to 71% of the recur-

rences occurred in the group of patients, where margins were not reported. According to national or local guidelines a close distance from DCIS to the superficial margin may as such not be acted upon and, as a consequence hereof, distance to the superficial margins may not be stated in the pathology report. In theory, re-resection of glandular tissue after SSM is not an option, since only skin and subcutis is expected to be overlying the area of potential concern. Performing a re-excision after NSM/SSM is also troublesome, and determining the precise location of the microscopically close/involved margin may be complicated. DCIS is often not visible macroscopically and despite meticulous documentation of the macroscopical examination, it may be difficult for the pathologist to pinpoint the exact location. This is further complicated by the fact that the surface of a SSM/NSM specimen has no distinct landmarks that enables specific localization of a pathological feature (Fig. 2F). The area of concern may also not be easily recognized for the surgeon at the second surgical procedure since the breast has been reconstructed and tissue rearranged.

Our report clearly demonstrates that the rate of involved or close superficial margins in SSM/NSM may as such be underestimated [12]. In an ongoing study by the Danish Breast Cancer Group (DBCG), the recurrence pattern in all danish patients diagnosed with DCIS from 2008–2017 is characterized and correlated to surgery type (Ethical committee 1-10-72-11-20).

Skin sparing/NSM and immediate reconstruction provide an important treatment option for breast cancer patients planned for mastectomy. Even though DCIS is a premalignant lesion with an excellent long-term survival irrespective of treatment, we recommend a careful preoperative evaluation to determine who are the patients that can safely undergo these procedures. Additionally, we recommend to carefully evaluate the superficial margins. In a systematic review examining the spatial location of LR after mastectomy, LRs were reported exclusively in the skin/ subcutaneous tissue in SSM /NSM with a shorter time of occurrence as compared to total mastectomies, drawing the attention towards the status of the superficial margin [30]. A thorough histopathological evaluation and reporting of residual disease as well as residual breast tissue at the superficial margin with SSM/NSM procedures will aid to obtain reliable clinical data on the risk of local recurrence and to improve the outcome of our patients [12]. The information is highly needed to be able to make sound decision on the need for re-resection (possibly including overlying skin), which is the preferred approach, or close follow up allowing for early detection of local recurrence in case of involved or close superficial margin.

The pros and cons of postmastectomy RT (of the reconstructed breast) in case of immediate reconstruction should be carefully evaluated. It is our recommendation that preoperative multidisciplinary assessment should support planning the surgical procedure to achieve clear margins rather than adding PMRT thereafter for incomplete resection. Regardless of the spatial location of the close/involved margins, Table 1 shows that close/positive margins in cases of mastectomy for pure DCIS are associated with risk of LRR, which is predominantly (>90%) invasive cancer [31,32]. Therefore, preoperative assessment is suggested to include careful evaluation of close lesion-to dermis distance and avoidance of SSM/NSM in case of unfavorable preoperative characteristics. Postoperative assessment should be performed, including reporting of the superficial margins with as precise a description as possible of where in the breast the close margin is located (e.g., with precise coordinates in relation to the nipple or base of the nipple as marked by the surgeon). If the positive margins are not excised at a second time, PMRT with additional boost to the area of involved margin (with bolus for superficial dose coverage, if needed), should be strongly considered [4,5].

Table 1
Recurrences after mastectomy for pure DCIS.

First Author (publication date)	Number of patients*	Median follow-up (months)	Definition of close/positive margins (mm)	Type of mastectomy	Type of mastectomy or reconstruction in LR/LRR group	Number of patients with close/positive margins	Number (%) of LR RR LRR DR	% LR/LRR in close margin group	Comments
Spiegel (2003) [33]	44	126	<1	NSM/SSM	n/a	6	0 LR	n/a	–
Carlson (2007) [26]	170**	82	≤1	SSM	expanders (3), TRAM (2) LD (2)	19	7 (4.1%) LR 2 (1.2%) RR 2 (1.2%) DR	10.5% (2/19)	Local excision revealed surrounding breast tissue in 6 out of 7 patients 6 were invasive recurrence
Rashtian (2008) [34]	80	61	≤2	SM (44), TM (9), MRM (18), SSM (2), Unknown (7)	SM (3) MRM (2) NSM (1)	31	5 (6.2%) LR 1 (1.2%) RR 3 (3.7%) DR	16% (5/31)	All recurrences were invasive carcinoma Mastectomy margins ≤ 2 mm were statistically significant for recurrence (16% vs. 2%)
Chan (2011) [35]	59	96	< 5	TM (39), SSM (14), total SSM (6)	SSM (1)	59	1 (1.7%) LR 1 (1.7%) LRR	3.4% (2/59)	One developed invasive cancer 20 years after the mastectomy and this was attributed to residual breast tissue
Chadha (2012) [36]	211	55	≤1	SM (39), TM (172) ***	n/a	24	1 (0.5%) LR 1 (0.5%) LRR	8.3% (2/24)	Both recurrences were invasive cancer Local excision revealed surrounding breast tissue
Owen (2013) [29]	637	144	<2	n/a	n/a	66	12 (1.9%) LR 2 (0.3%) RR 7 (1.1%) DR	4.5% (3/66)	91.6% of recurrences were invasive Age < 40 years was found to be significant factor for LR
Childs (2013) [37]	142	91	≤2	SSM (83)	SSM (1) SSM/TRAM (1)	44	1 (0.7%) LR 1 (0.7%) LRR & DR	4.5% (2/44)	Both LR were in cases of SSM All recurrences were invasive
Fitzsullivan **** (2013) [4]	810	76	≤1	SSM (470)	n/a	94	8 (1%) LRR 3 (0.4%) DR	5.3% (5/94)	SSM, immediate reconstruction were significant risk factors for close margins Mastectomy margins were significant for LRR (5% for margins ≤ 1 mm, 3.6 % for margins 1.1–2.9 mm, and 0.7 % for margins ≥ 3 mm [p < 0.001]) None of the patients who had LRR received PMRT
Clements **** (2015) [5]	2944 (margins reported in 925 only)	61	<2	n/a	n/a	177 (of 925)	23 (2.5%) LR 3 (0.3%) RR 19 (2.0%) DR	1.7% (3/177)	32/45 (71%) recurrences occurred in patients, where margins were not reported In the group with known margins, all LRR were in patients who did not receive PMRT In the group with margins not reported, 97% of LRR were in patients who did not receive PMRT
Timbrell (2016) [24]	199	65	<2	SSM (102) SM (97)	SSM (8), 7 had IBR SM (0)	57	8 (4%) LRR	8.8% (5/57)	92% of LRR were invasive 31% SSM had involved margins 26% SM had involved margins All recurrences were invasive

*Number of pure DCIS patients who underwent mastectomy. The surgeries are named according to the study definition.
 **The study included a total of 223 patients, but only 170 patients had complete data for analysis. Recurrence rates are based on 170 patients.
 ***In the discussion it is stated that some had SSM but the number is not clearly indicated.
 ****Included patients who were treated with PMRT for close/positive margins.
 SSM – skin sparing mastectomy; NSM – nipple sparing mastectomy; MRM – modified radical mastectomy; SM – simple mastectomy; n/a – not applicable; LR-local recurrence i.e., chest wall recurrence; RR – regional recurrence, lymph nodes; LRR-locoregional recurrence, i.e., chest wall and/or lymph nodes; DR – distant recurrence; IBR – immediate breast reconstruction; PMRT – postmastectomy radiation; LD – Latissimus Dorsi based reconstruction; TRAM – Transverse rectus abdominis muscle based reconstruction.

Conflict of interest

Declarations of interest: none.

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The clinical data incl. pictures have been fully anonymized, and informed consent not required.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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