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Surgical Research

Oncological Safety of Skin-Sparing Mastectomy and Immediate Breast Reconstruction in Extensive Ductal Carcinoma In Situ

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ARTICLE INFO

ABSTRACT

Introduction: Skin-sparing mastectomy (SSM) with immediate breast reconstruction is the ideal treatment for interested and suitable patients with extensive ductal carcinoma *in situ* (DCIS). There is no guideline to indicate on how large DCIS the procedure can be performed safely. The primary target of this study was to define the oncological safety of SSM in extensive pure DCIS. The secondary target was to find predictive factors for DCIS upstaging to invasive disease.
Materials and methods: A total of 71 consecutive patients with extensive pure DCIS and undergoing SSM with immediate latissimus dorsi (LD) breast reconstruction were retrospectively evaluated.
Results: The median size of DCIS lesion in preoperative imaging was 60 mm, the median weight of mastectomy specimen was 350 g, and the median resection margin (RM) was 2.0 mm. A total of 20 patients (28%) had an RM less than 0.5 mm and nine patients (13%) had ink positive margins. Six patients having positive RM underwent reoperation. A total of 29 patients (41%) presented invasive cancer foci in final histopathological assessment and nine patients (13%) had an axillary metastasis. Adjuvant therapy was given to 23 patients presenting invasive cancer. There were no local recurrences or distant metastases (0%, 95% confidence interval 0-0.051) during the mean follow-up of 71 mo. None of the factors evaluated predicted upstaging to invasive disease.
Conclusions: SSM with immediate breast reconstruction in patients with extensive DCIS is oncologically safe even when the margins are close or positive. Additional invasive foci and solitary axillary lymph node metastases are frequent but do not worsen the outcome.

Introduction

Ductal carcinoma *in situ* (DCIS) is a preinvasive form of breast cancer, in which the cancer cells do not penetrate the ductal basement membrane. Therefore, it is considered a stage in which cancer is not yet able to spread regardless of the size of the DCIS lesion.[1] When the tumour-to-breast size-ratio of the DCIS lesion allows breast conserving surgery, it is usually performed.

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However, DCIS has frequently separate foci away from the primary lesion, which emphasizes the importance of meticulous removal of the affected breast tissue.[2] As per the treatment guidelines, the DCIS lesion should be removed with at least a 2-mm resection margin (RM).[3,4] When the DCIS lesion is extensive, multicentric, or the tumour-to-breast volume ratio is high, mastectomy is generally mandatory.[1] Furthermore, 8%-59% of patients who have preoperatively been assessed to have a pure DCIS lesion, turn out to have an invasive component in the final histopathological assessment of the surgical specimen[5-10] and 3%-15% present with an axillary metastasis.[11-15] The reported rate of upgrade is highly varying, but the risk of upgrade seems to be higher in patients with symptomatic DCIS, as in a meta-analysis including fifty two studies and 7350 patients with DCIS, the median risk of upgrading was 26%, but as high as 46% in patients presenting with symptomatic DCIS (as opposed to asymptomatic, screening detected DCIS).[10] When breast conserving surgery is performed and an invasive component is found in the histopathological assessment, performing sentinel node biopsy (SNB) is indicated. As SNB cannot be reliably performed after mastectomy, it is advisable to be performed at the same time with the mastectomy.[15]

For a patient undergoing a mastectomy for extensive DCIS, but interested in a breast reconstruction, the optimal management is a skin-sparing mastectomy (SSM) or a nipple-sparing mastectomy with immediate breast reconstruction.[1] Immediate breast reconstruction has several benefits compared to mastectomy and delayed reconstruction, as the patient only needs a one-stage surgery and the aesthetic and psychological outcomes appear to be improved.[16,17] However, there are no guidelines to indicate in which patients and on how large DCIS the SSM can be performed safely.[18]

In case the postoperative histopathological assessment would reveal invasive breast cancer, adjuvant therapies are considered. If breast implant has been used with the latissimus dorsi (LD) flap, the benefits and risks of radiotherapy should be discussed by the multidisciplinary breast cancer team.

The main challenge with SSM and immediate reconstruction in oncological perspective is the anterior RM toward the spared skin envelope, which often proves to be scarce. In surgery the surgeon is balancing between a thin skin flap, which compromises the blood supply of the skin, and a thicker flap, with a risk of leaving a residual breast tissue and performing a noncomplete excision of the tumor.[19]

At our institution, the vast majority of immediate breast reconstructions have been performed with a LD myocutaneous flap, with or without implants. The primary target of this study was to define the oncological safety of SSM with immediate LD reconstruction for extensive DCIS in terms of local recurrence (LR), loco-regional recurrence (LRR), and distant recurrences. Secondary target was to evaluate whether it is possible to find predictive factors for DCIS upstaging to invasive cancer in case of extensive DCIS.

Materials and Methods

All patients undergoing SSM and immediate breast reconstruction with LD flap (with or without an implant) for extensive DCIS between January 2010 and December 2019 were included in this retrospective study at the Department of Plastic and General Surgery, Turku University Hospital. In this study, the definition of extensive DCIS was based on preoperative breast imaging studies (mammography, ultrasound, and/or magnetic resonance imaging [MRI]) and preoperative core needle biopsy. If the size of DCIS was estimated to exceed the tumour-to-breast size-ratio that would allow breast conserving surgery, it was estimated as extensive. The research protocol of the study was approved by Hospital District of Southwest Finland (T218/2019). The study was conducted retrospectively from data obtained for clinical purposes and a waiver of informed consent was approved by the institutional review board.

Patients were diagnosed with DCIS in primary healthcare and referred to the surgical unit. All patients who had a large pure DCIS requiring mastectomy and considered eligible for immediate breast reconstruction were referred to a plastic surgeon. Turku University Hospital is the only hospital of the region (Hospital District of Southwest Finland) where such patients are referred, so selection bias should not exist.

The patients not interested or not eligible to have a breast reconstruction underwent a simple mastectomy. All patients were postoperatively discussed at a multidisciplinary meeting (comprising surgeons, pathologists, radiologists, and oncologists) which also determined whether reoperation or adjuvant treatment was necessary.

The patient information was acquired from the Hospital District's database. Patients with a diagnosis code of DCIS and an operation code of immediate breast reconstruction were reviewed. Patients having previous breast surgeries were excluded. Any excisional surgery was considered a previous surgery. A core needle biopsy was not considered a previous surgery and surgical biopsy is very rarely performed in our hospital. The patient data and information on preoperative imaging findings, preoperative biopsy samples, and postoperative histopathological reports reviewed. The size of the DCIS lesion in imaging studies and histopathological assessment, RM width, sentinel node findings, and presence of invasive breast cancer foci were recorded. The number of reoperations in the case of close or positive RM and the use of adjuvant therapy in the patients with invasive cancer were recorded. The rate of postoperative skin healing problems, such as skin necrosis, were recorded to ensure that the recurrence rate was not diminished by making the anterior skin flap excessively thin and thus causing skin healing problems.

Surgical technique

In total eight plastic or breast surgeons with several years of experience as a consultant surgeon performed the SSM and axillary operations. All reconstructions were unilateral and performed by an experienced plastic surgeon. All patients had the nipple-areola complex removed. An elliptical incision fitted to the patient's anatomy was used. The mastectomy was performed leaving the anterior skin flap approximately 5 mm thick. The inframammary fold was preserved. The fascia of pectoralis muscle was removed. The LD myocutaneous flap was used for all patients. When an implant was needed to achieve an adequate breast volume, definite implants were used. In some cases, a symmetric mastopexy or breast reduction surgery was performed by another plastic or breast surgeon.
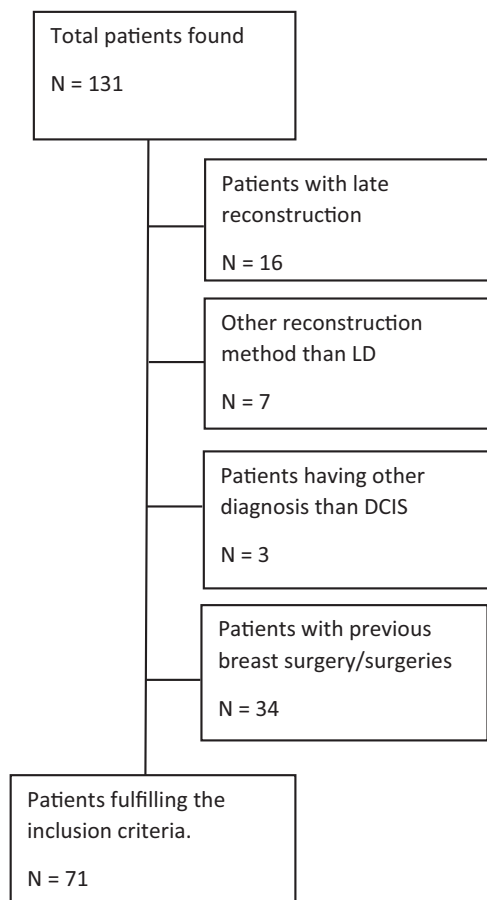
Fig. — **Flow chart illustrating the study population selection.**

Table 1 — **Patient characteristics and clinical findings related to the DCIS. All numbers are given as (n, %) unless otherwise specified.**

Total number of patients	71
Age (y)	57 (51-63)[*]
BMI (kg/m^2)	24.4 (22.0-29.0)[*]
DCIS size in imaging (mm)	60 (45-80)[*]
Preoperative MRI performed	50 (70%)
Manner of presentation	
Asymptomatic	45 (63%)
Symptomatic	26 (37%)
Palpable mass	10 (14%)
Nipple discharge	10 (14%)
Mammary Paget's disease	3 (4%)
Nipple retraction	2 (3%)
Mastitis	1 (1%)

BMI = body-mass index; DCIS = ductal carcinoma *in situ*; MRI = magnetic resonance imaging.
[*]Median and interquartile range.

Follow-up

The patients having adjuvant therapy were followed up for 5 y at the Department of Medical Oncology and Radiotherapy, Turku University Hospital. The follow-up consisted of an annual clinical examination and a mammography of the contralateral breast. The patients not having an adjuvant therapy were followed up with the same protocol in primary healthcare annually until the age of 50 y and biannually after the age of 50 y. The same protocol was used for the patients having adjuvant therapy after the 5-y follow-up in tertiary healthcare.

During the follow-up, the number and type of recurrences and deaths were recorded.

Statistical methods

A statistical analysis was performed to reveal any associations between preoperative characteristics and the risk of upstaging of DCIS to invasive cancer. Frequency tables were analyzed with a Fisher's exact test and continuous variables were compared with a Mann—Whitney *U*-test. The confidence interval for the risk of recurrence was determined using binomial exact value calculation. For the upper limit of the risk of recurrence, one-sided 97.5% confidence interval was used. JMP Pro 15 (SAS Institute, Cary, North Carolina) was used to conduct the statistical analysis.

Results

An inquiry to the Hospital District's database returned information of 131 patients who were recorded to have a diagnosis of DCIS and who had a breast reconstruction in years 2010-2019. The evaluation of the patient records revealed 60 patients who did not meet the inclusion criteria (Fig.). A total of 71 patients were found to have a correct diagnose of DCIS and who underwent an immediate breast reconstruction with LD flap. There were seven patients who underwent the immediate breast reconstruction with other techniques than LD flap, and thus 91% (71/78) of the procedures were performed with the LD flap. No patient was excluded due to a previous surgical biopsy.

Patient characteristics

The median age of patients was 57 y. A total of 45 patients (63%) presented with a screen-detected asymptomatic DCIS and 26 patients presented with various symptoms (Table 1). All patients underwent a mammography, and 50 patients (70%) had an additional MRI study. All patients had a diagnostic core needle biopsy showing DCIS with no invasive disease. The median size of the DCIS lesion detected in the imaging study was 60 mm (range: 28-160 mm). Overall, 92% of the patients (65 of 71) had a DCIS diameter of at least 40 mm. Three smallest diameters of the DCIS lesion were 28 mm, 33 mm, and 35 mm in small-sized (mastectomy specimen weight less than 200 g) breasts.

All patients were examined by experienced consultant surgeons. Ten patients were detected to have a palpable tumor and 27 patients had no abnormal findings in examination. The remaining 34 patients had mild palpable "firmness" but no tumor, which usually was due to the hematoma after the core needle biopsy.

Table 2 – Factors associated with invasion *versus* no invasion found in histopathological assessment. All numbers are given as (*n*, %) unless otherwise specified.

Factor	Invasion (29)	No invasion (42)	P value
Age (y)	54.3 (48.0-62.5)[*]	58.4 (53.8-64.0)[*]	0.15
Mastectomy specimen weight (g)	399 (272-553)[*]	337 (276- 564)[*]	0.50
Preoperative MRI			0.33
No MRI	11 (52%)	10 (48%)	
MRI	18 (36%)	32 (64%)	
DCIS diameter (mm) in preoperative imaging	75 (45-90)[*]	56 (45-80)[*]	0.18
Grade			0.34
I	2 (22%)	7 (77%)	
II	9 (53%)	8 (47%)	
III	16 (41%)	23 (59%)	
Manner of presentation			0.89
Asymptomatic	17 (32%)	28 (62%)	
Lump	5 (50%)	5 (50%)	
Nipple discharge	4 (40%)	6 (60%)	
Mammary Paget's disease	2 (67%)	1 (33%)	
Nipple retraction	1 (50%)	1 (50%)	
Mastitis	0 (0%)	1 (100%)	
Body Mass index (kg/m^2)			0.24
Normal (18.5-25)	13 (34%)	25 (66%)	
Overweight (25-30)	6 (40%)	9 (60%)	
Obese (over 30)	9 (60%)	6 (40%)	

MRI = magnetic resonance imaging; DCIS = ductal carcinoma *in situ*.
[*] Median and interquartile range.

Details of surgery

All patients underwent SSM and immediate breast reconstruction with an LD flap, with an implant (43 patients) or without (28 patients). All but one patient underwent SNB with frozen section study and an immediate axillary lymph node dissection (ALND) was performed in the patients presenting metastatic axillary lymph nodes as per the guidelines of that time.

One patient had an unsuccessful SNB, and ALND was performed revealing only normal lymph nodes in the histopathological assessment. Two of the patients had isolated tumor cells (ITC), three patients had a micrometastasis (0.2-2.0 mm), three patients had a single macrometastasis (>2 mm), and one patient had metastasis in two of the lymph nodes in the SNB. In total, 10 patients (14%) underwent ALND. Three of the 10 patients having ALND presented with one additional nonsentinel node metastasis and the remaining seven had only normal lymph nodes.

Two patients with ITC had no invasion found in the mastectomy specimen. All others with positive SNB had invasive breast cancer detected in a postoperative histopathological assessment.

Postoperative histopathological assessment

The histopathological assessment revealed invasive cancer in 29 patients (41%). None of the clinical or histopathological factors, or performing an MRI preoperatively, could predict the finding of an invasive cancer (Table 2). Nine patients had a multifocal or multicentric cancer. The size of invasive foci was usually small (median 6.5 mm; range: 1-26 mm)

The median diameter of the DCIS lesion in a histopathological assessment was 54 mm (interquartile range: 37-80 mm). The median RM was 2.0 mm, with 41 (58%) patients having RM of ≤ 2 mm, 20 patients (28%) having RM less than 0.5 mm, and nine patients having positive RM (Table 3).

Patients with positive resection margins and invasive cancer

Close but negative RM (≥ 0.1 mm) were interpreted as sufficient and not demanding reoperations as all the breast tissue was supposedly removed. Nine patients had positive RM and these patients and the adjuvant therapies they

Table 3 – Distribution of smallest histopathological margins. Numbers are given as (*n*, %).

Smallest histological margin (mm)	N
0	9 (13%)
0.1-0.5 mm	11 (15%)
0.6-1.0 mm	6 (8.5%)
1.1-2.0 mm	16 (23%)
2.1-5 mm	12 (17%)
5.1 mm->	17 (24%)

Table 4 — Patients with zero-margin in histopathological assessment.

Pt	DCIS width	Direction of 0-margin	Reoperation	Invasive disease	Adjuvant treatment	Multifocal invasion	SLNB	Axillary status	Follow-up (mo)
1	120 mm	Lateral	Yes	Ductal	yes[*]	yes	Macro	2/21	37
2	21 mm	Skin	Yes	Lobular	yes[†]	no	0	0/3	56
3	50 mm	Skin	Yes	Ductal	no	no	0	0/1	112
4	86 mm	Lateral	Yes	Ductal	yes[‡]	yes	Macro	3/17	60
5*	80 mm	Lateral	Late	No	yes[§]		0	0/4	58
6	26 mm	Medial	No	No	No		0	0/3	50
7	150 mm	Skin	Yes	No	No		0	0/4	78
8	59 mm	Skin	Yes	No	No		0	0/4	59
9	87 mm	Skin	No	No	No		0	0/4	29

DCIS = ductal carcinoma *in situ*; SLNB = sentinel lymph node biopsy; RT = radiation therapy; CT = chemotherapy; HT = hormonal therapy.
Patient underwent an MRI and had an RT before reoperation. Reoperation confirmed only fibrosis.
[*] RT, CT, HT.
[†] CT, HT.
[‡] RT, CT, HT, trastuzumab.
[§] RT.

underwent are represented in Table 4. Six of these patients underwent a reoperation by the decision of a multidisciplinary meeting. The histopathological assessment of the re-excised tissue revealed no residual DCIS in four of the patients. Two patients, having the re-excision on the anterior margin, had a residual DCIS detected but this time with negative RM. One patient (Table 4, patient 5) with positive RM underwent an MRI, which presented convincing findings of a residual DCIS. Patient was prescribed radiation therapy. The MRI was repeated after the radiation therapy, showing no more DCIS specific enhancement. Reoperation was performed for certainty and the histopathological assessment of the excised tissue revealed no malignant findings but only fibrosis. The patient has not had a recurrence in a close follow-up of 58 mo.

Of the 29 patients presenting invasive cancer, 23 received an adjuvant therapy. Six of the patients had no adjuvant therapy since they had no axillary metastases and the invasive lesion was small (mean size 4.9 mm; range: 1.7-9.5 mm). Three of the patients not having invasive cancer underwent radiotherapy due to minimal RM. Two patients were prescribed a hormone therapy.

Complications

Six patients (8.4%) suffered postoperatively a partial skin flap necrosis. Two of them required reoperation and four of them had a minor necrosis requiring only a topical treatment.

Follow-up

The follow-up information was updated in August 2021. The mean follow-up time was 71 mo (median: 68 mo, interquartile range: 46-94 mo). None of the patients had a local recurrence nor distant metastases during the follow-up (0%, 95% confidence interval [CI] 0-0.051).

One of the patients, presenting primarily with an invasive ductal HER2-positive carcinoma, developed a lobular type HER2-negative carcinoma on the contralateral breast found in a 4-y control mammography.

One patient died of mesothelioma at 86 mo from the breast cancer surgery.

Discussion

In this study, it was shown that positive or close margins after SSM do not necessarily imply a high rate of local recurrence, even when the DCIS lesion is extensively compared to size of the breast. This was not affected by the fact that a notable portion of the patients (41%) presented with an invasion in the postoperative histopathological assessment. Despite the high proportion of invasive cancer, surprisingly, there were no recurrences during the mean follow-up time of 6 y. We conclude that SSM has no elevated risk of local or distant recurrence when compared to traditional mastectomy and can therefore be safely performed.

The reported incidence of LR and LRR after the SSM is highly variable (0%-24%).[20-25] Three studies considering only SSM and pure DCIS present LR of 1.0%, 3.3%, and LRR of 5.9%, but in all of these studies the size of the DCIS lesion has been notably smaller and RM wider than in this study.[26-28] A recent meta-analysis of a simple mastectomy in pure DCIS showed an LR of 5.3% in the positive or close RM group, where an RM of <1 mm (four studies) or <2 mm (eight studies) were considered close ones, and 1.6% when the RM was negative.[29] In those studies, in which the recurrence rate has been determined for an RM less than 1 mm, the recurrence rates have been higher: 5.3%,[30] 8.3%,[31] and 10.5%.[28] Furthermore, it has been shown that upstaging to an invasive disease is associated with a higher risk of recurrence.[32] Most studies have also excluded the patients with an invasion found in the histopathological assessment, and therefore these studies are not comparable with the present one. A meta-analysis considering SSM in both DCIS and invasive cancer presents an LR rate of 6.2%.[33]

Most studies show the median time from the surgery to the recurrence to be 36-57 mo.[25,26,30,32,33] In the present study, the mean follow-up time is 71 mo (median: 68 mo), which exceeds the average recurrence time in the previous studies.

SSM has a risk of two conflicting complications: either having an insufficient RM resulting in a reoperation, adjuvant radiotherapy, or having an increased risk of local recurrence and on the opposite side, having a skin flap necrosis resulting in a delayed wound healing, reoperations, and a worse aesthetic outcome. In the present study, both positive margins (13%) and skin flap necrosis (8%) were detected. Reoperations were performed in six patients (8.5%) due to a positive RM and in two patients (2.8%) due to a skin flap necrosis. Four of the six patients suffering from skin flap necrosis had a minor necrosis demanding only a topical treatment. The overall number of skin necrosis is in concordance with the previous literature showing a necrosis rate of 0%-17%.[34-38] The dilemma is associated with the surgical technique of SSM, the thickness of skin flaps, and the amount of a residual breast tissue left especially on the anterior margin. Contradictory to each other, it has been shown that the skin flap thickness more than 5 mm increases the amount of residual breast tissue[39] and the flap thickness less than 5 mm increases the risk of skin necrosis.[40] Based on these studies and results of the present study, it can be concluded that the 5-mm skin flap thickness is close to the optimal when performing SSM.

In our study, it was also discovered that extensive DCIS lesions have a frequent tendency (41%) to be upstaged to an invasive carcinoma in the final histopathological assessment and that there is no reliable method on predicting which patients come up with the invasive disease. The assumption that a palpable tumorous DCIS should have a higher probability of upstaging did not get support by this study. Patient characteristics, symptoms, the histopathological assessment of core needle biopsy, or imaging studies were not able to discriminate an invasive and a preinvasive disease from each other. It should be noted that although the majority of patients presented with no symptoms and that the disease was usually found in the screening mammography, more than one-third (37%) of the patients presented with a symptom leading to investigations. The symptoms were similar to the ones that breast cancer patients usually present with (lump, nipple discharge, nipple retraction, and Mammary Paget's disease), but in the statistical analysis, none of the symptoms showed a prognostic value for finding an invasive cancer.

In this study, one of the patients developed breast cancer to the contralateral breast. Meijnen *et al.* reported the risk of contralateral breast cancer for patients who underwent mastectomy for DCIS to be 6.5% in 8 y of surveillance.[41] The single case in our study would seem to be in concordance with this previous estimation.

Two of the patients had an ITC found in the SNB, but no invasive cancer was found in the mastectomy specimen, although a close re-examination was performed. Similar results have been shown before[11,12] and the probable interpretation is that the invasive focus merely was not found in the histopathological assessment. It has also been suggested that the core needle biopsy used in diagnostics could lead to detaching of the tumor cells and dissemination of the cancer to the sentinel lymph nodes.[42] This theory, however, has not been supported by later research.[43-45] Another, although theoretically hardly explainable possibility would be, that the DCIS lesion would have a potential to spread and generate metastasis. The latter seems improbable and would not have a simple method of being proved.

Limitations

Limitations of the present study include its retrospective nature. A major limitation of the study is the limited number of patients, resulting from the small number of patients presenting with a pure extensive DCIS. It would be interesting to see whether similar results could be achieved in a larger study.

The mean follow-up time in this study is 71 mo, which is more than the average time from surgery to recurrence in the previous literature, but it is not possible to make a conclusion that none of the patients would develop a recurrence later. We will continue the follow-up to discover any late recurrences. In Finland, the hormonal receptors are not examined in DCIS, as endocrine treatment is not used for pure DCIS, so the information was not available to be considered in the analysis.

The patients having positive RMs had various numbers of reoperations and varying adjuvant therapies, making the evaluation of the effect of these procedures difficult.

Conclusions

In conclusion, SSM with immediate breast reconstruction in patients with extensive DCIS is oncologically safe, even with close RMs. Additional invasive foci or solitary axillary lymph node metastases do not seem to worsen the outcome.

Author Contributions

Disclosure

Funding

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