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Oncological outcomes after simple and skin-sparing mastectomy of ductal carcinoma in situ: A register-based cohort study of 576 Norwegian women

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ABSTRACT

Background: For Ductal Carcinoma in Situ (DCIS), recurrence is shown to be higher after skin-sparing (SSM) versus simple (SM) mastectomy. This study aimed to compare the two groups recurrence rates, disease-free survival (DFS), and overall (OS) survival.

Methods: We conducted a retrospective register-based cohort study of women operated with SSM (n = 338) or SM (n = 238) for DCIS between 2007 and 2017. Data from the Norwegian Breast Cancer Registry was used to estimate recurrences rates, DFS and OS.

Results: Mean age was 51 and 61 years in the SSM and SM groups, respectively. Median follow-up time was 77 months for SSM (range: 21–152 months) vs 84 months for SM (range: 7–171 months). After five years of follow-up, the overall recurrence rate (OR) was 2.1%; 3.9% for SSM and 0.9% for SM. After ten years, the rates were 3.0%, 6.2% for SSM and still 0.9% for SM. DFS was after ten years 92.2%; 91.8% for SSM, and 92.4% for SM. OS was 95.0%; 97.5% for SSM and 93.3% for SM at ten years. For SSM, involved margins represented a significant risk for recurrence.

Conclusion: The recurrence rate was higher in the SSM versus the SM group. Whether the difference is due to the operating procedures or underlying risk factors remains unknown. When stratifying for the difference in age, there was no statistical difference in DFS or OS. Involved margins in the SSM group were associated with an increased risk of recurrence.

1. Introduction

Ductal carcinoma in situ (DCIS) is a non-invasive lesion of malignant epithelial cells within the breast. It ranges from low-grade lesions that are not life-threatening to widespread high-grade lesions which may contain invasive disease [1]. DCIS is often associated with clinical and mammographic inapparent disease [2] and represents approximately 20% of screen-detected malignancies [3,4]. The primary aim of treatment is to reduce the risk of invasive recurrence [5]. Mortality in DCIS patients is low [6,7].The standard of care involves breast-conserving surgery with radiation therapy (RT) [5]. RT reduce the risk of recurrence by approximately 50% [8,9]. Mastectomy is

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chosen when the size of DCIS does not allow for cosmetically acceptable breast-conserving surgery, widespread disease, gene mutation carriers and if the woman prefers. RT is not a standard treatment after mastectomy but can be used if surgical margins are widely involved [5]. Whether it is required is subject to some controversy [10]. Locoregional recurrence after mastectomy is between 1 and 3% [11,12]. In simple mastectomy (SM), the entire breast is removed with an ellipse of the overlying skin. Different surgical methods have been introduced to improve cosmetic results and reduce the side effects of the treatment. In skin-sparing mastectomy (SSM), the skin coverage of the breast is preserved, enhancing the cosmetic results of breast reconstruction. The breast is reconstructed with tissue either from another body location or with an implant. These operations have evolved substantially since they were introduced in the late 90thies. Preservation of the nipple in nipple-sparing mastectomies and pre-pectoral instead of sub-pectoral positioning of the implant are examples. Immediate breast reconstructions significantly benefit patients' quality of life [13,14]. There has been a concern that resecting less skin compromises the mastectomy's completeness with 1.5–5.9% local recurrence rates reported [15–20]. However, studies with small sample sizes and a lack of data challenge efforts to quantify the difference in risk. To increase the knowledge gap, we took advantage of the data collected in the Norwegian Breast Cancer Registry which includes data related to potential confounders and conducted a study that aimed to compare recurrence rates, disease free- and overall survival among women diagnosed with DCIS and treated with SSM versus SM in Norway.

2. Material and methods

The study was approved by the Regional Committee for medical and health research ethics in Norway (approval number 11134) and received an exemption for informed consent. It has been mandatory by law since 1953 to report all cancer cases to the Cancer Registry of Norway (CRN), ensuring complete data capture of all cancer diagnoses [21]. Norwegian clinical departments register in the CRN's electronic reporting service. The Norwegian Breast Cancer Registry (NBCR) gained national status in 2013. Data on histopathologic characteristics of the tumors are reported from pathology departments. Since 1997, the CRN has retrospectively retrieved data from all Norwegian radiotherapy centers. In this study, we received data on age, detection mode (screen-detected, symptomatic, private institute, high risk, and other), surgical treatment, histopathology, radiotherapy, recurrence status, and death from the CRN. All individuals in Norway are assigned a unique personal identification number at the time of birth or immigration. This number was used to link data across databases and provide complete information for the individuals.

2.1. Variables

This is a retrospective study of women diagnosed with DCIS in Norway from 2007 to 2017. We received pathology data of 4288 women diagnosed with DCIS during the study period. 1031 underwent mastectomy and constitute the study population. We excluded data on 32 women with previous breast cancer and 473 without information on surgical procedures, leaving 576 women in the study sample (Fig. 1).

NBCR is designed with nine clinical reporting modules. A separate notification is submitted for every event during diagnosis, treatment, and follow-up. The modules are used for primary breast cancer treatment, local and regional relapses, and metastatic disease. If breast-conserving surgery was performed before mastectomy, mastectomy was used as the surgical treatment. There was incomplete information about the nipple and areola complex preservation, and women with reconstruction were categorized into one group, SSM. All patients in the SSM group underwent primary implant-based breast reconstruction in one or two stages. Immediate autologous breast reconstruction is not performed in Norway. The women were categorized into groups by detection mode, age, and the DCIS according to size reported by the pathologists in the pathology reports. Van Nuys' system was used for grading [22]. If a patient had undergone several operations, the total DCIS diameter was defined as the sum of DCIS diameters and histological grade as the maximum value across all surgery. We received information about the closest resection margins between DCIS, the chest wall (back), and the specimen's sides. An involved surgical margin was defined as < 2 mm at the sides and 0 mm against the chest wall. The margins at final surgery were used in patients with several surgeries. The margins were reported according to side, back, and any (back or side or both).

2.2. Recurrence and time to follow-up

Follow-up time for recurrence and death was defined as the time from the final surgical procedure until the data extraction from the registry in May 2021. Recurrence of disease was retrieved from the database with information on time (month and year), histopathology, and location. The recurrence was categorized as local recurrence (LR), locoregional recurrence (LRR), nodal recurrence (NR) and distant recurrence (DR). Local recurrence could be DCIS or breast cancer. Patients with no pathological or clinical information about recurrence in the registry at the time of extraction of data were classified as recurrence-free.

2.3. Statistical analysis

The data were analysed using Stata version 17.0 and R version 4.1.2. The Student's t-test with 5% significance level was used to compare the values of continuous variables between the SM and SSM groups. For categorical variables, Pearson's chi-squared test was used. Overall survival (OS) was defined as the time from final primary surgery until death, while disease-free survival (DFS) was defined as the time to either LR/LRR/NR/DR or death, whichever comes first until data extraction from the registry. Inverse probability weighting (IPW) was performed for the variable “Age”. The resulting weights were used to perform weighted Kaplan Meier plots with OS and DFS as separate outcomes. The log-rank test was used to compare the survival of the two groups. Univariate Cox regression was used to identify risk factors within the SSM group.

The study has used data from the Cancer Registry of Norway (CRN). The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

3. Results

A total of 338 (58.7%) women had an SM and 238 (41.3%) SSM. They were operated at 21 different hospitals and the number of operations at each hospital varied between 2 and 164. We found 254 (44.1%) to be screen-detected, 184 (31.7%) symptomatically, and the rest, 16.1%, in other categories or missing (Fig. 1). The mean age was 51 years in the SSM group and 61 years in the SM group ($p < 0.001$). The mean total DCIS diameter in the SSM group was 45 mm and 39 mm for those operated with SM ($p = 0.017$). There was involved side margins in 22.3% in the SSM group compared to 9.4% in the SM group ($p < 0.001$). No differences were noted between histologic grade ($p = 0.262$) and involved back margins in the two groups (4.7% vs 3.0% $p = 0.331$). Postoperative radiation therapy was delivered to 9.2% (22/238) of the women in the SSM

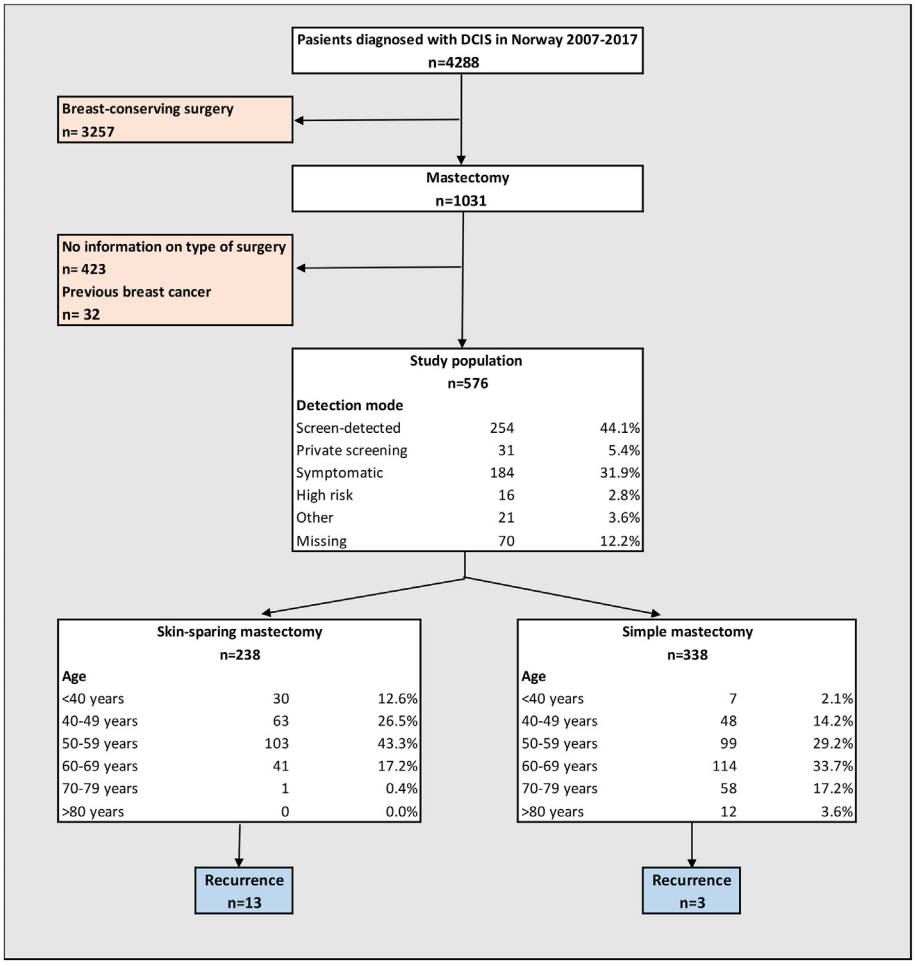

Fig. 1. Flowchart of the study population.

group and 3.3% (11/338 in the SM group (p = 0.002) (Table 1). RT was delivered to 21% (7/33) of the women with free margins and 26% (22/83) of those with involved margins.

The proportion of women operated with SMM was 50% in 2016, while none received such treatment in 2007 (Fig. 2). Follow-up time was shorter in the SSM group, with a median follow-up time of 77 months (range: 21–152 months) compared to 84 months (range: 7–171 months) in the SM group.

During the 10-year analysis period, 15 women recurred, 12 in the SSM group and 3 in the SM group (Table 2). In the SSM group, 4 women had involved side margins, and 2 involved back margins after primary surgery. One woman who was radiated after primary surgery due to involved margins recurred. In the SM group, 1 woman had an involved side margin, and one had an involved back margin; none were radiated. We found most of the recurrence to be local; 10 were LR, 4 LRR and 1 NR. Only 1 woman presented with distant metastasis. The median time from operation to the first recurrence was 30 months (range 11–86 months), 32 months in the SSM group (range 21–86 months) and 15 months in the SM group (range 11–34 months). After LRR, one woman experienced DM after 12 months. Half of the recurrences were infiltrating carcinomas.

Using univariate Cox regression in the SSM group, lack of free resection margins were the only significant risk factor for recurrence (Table 3). A direct statistical evaluation of the difference in recurrence between hospitals was prohibited by the small number of operations at some hospitals and few events.

Kaplan-Meier analysis demonstrated that the overall recurrence rate for all patients in the dataset was 2.1% after five years and 3.0% after ten years; 3.9% in the SSM group after five years compared to 0.9% in the SM group. Ten-year recurrence rate was 6.2% in the SSM group and 0.9% (identical to 5 years) in the SM group. A direct statistical evaluation of the difference in overall recurrence between the two groups was prohibited by the competing risk relation of death and recurrence, combined with the small number of recurrent events.

In total, 36 patients died during follow-up: 5 in the SSM group and 31 in the SM group. Most of them (31/36) died of other diseases than breast cancer. Disease-free survival in the entire population after five years was 93.9%; 94.0% in the SSM group and 93.8% in the SM group. At ten years, DFS in the entire population was 92.2%; 91.8% in the SSM group and 92.4% in the SM group (Fig. 3b). The overall survival in the entire population at five years was 95.0%; 97.5% in the SSM group and 93.3% in the SM group. At ten years, the OS in the entire population was 95,0%; 97,5% in the SSM group and 93,3% in the SM group (Fig. 3d). There was no statistically significant difference in DFS or OS between the two groups when adjusting for patient age with inverse probability weighting (Fig. 3a and c).

Table 1
Descriptive characteristics of women diagnosed with DCIS operated with mastectomy or skin-sparing mastectomy in Norway 2007 to 2017.

	Information on surgery available		Skin-sparing mastectomy		Simple mastectomy		p-value
	(n)	(%)	(n)	(%)	(n)	(%)	
DCIS cases	576		238	41,3%	338	58,7%	
Recurrence	15		12		3		
Age							
<40 years	37	6,4%	30	81,1%	7	18,9%	
40–49 years	111	19,3%	63	56,8%	48	43,2%	
50–59 years	202	35,1%	103	51,0%	99	49,0%	
60–69 years	155	26,9%	41	26,5%	114	73,6%	
70–79 years	59	10,2%	1	1,7%	58	98,3%	
>80 years	12	2,1%			12	100,0%	
Mean	**56**		**51**		**61**		**p < 0,001**[a]
DCIS diameter							
≤10 mm	45	7,8%	24	53,3%	21	46,7%	
11–20 mm	67	11,6%	29	43,3%	38	56,7%	
21–30 mm	84	14,6%	22	26,2%	62	73,8%	
31–40 mm	71	12,3%	20	28,2%	51	71,8%	
41–50 mm	66	11,5%	33	50,0%	33	50,0%	
51–60 mm	46	8,0%	14	30,4%	32	69,6%	
61–70 mm	50	8,6%	31	62,0%	19	38,0%	
71–80 mm	39	6,8%	18	61,1%	21	53,6%	
81–90 mm	18	3,1%	11	55,0%	7	38,9%	
91–100 mm	14	2,4%	6	42,9%	8	57,1%	
>100 mm	20	3,5%	11	55,0%	9	45,0%	
Information not available	56	9,7%	19	33,9%	37	66,1%	
Mean	**41**		**45**		**39**		**p = 0,017**[a]
van Nuys' grade							
1	52	9,0%	26	50,0%	26	50,0%	
2	50	8,7%	17	34,0%	33	66,0%	
3	448	77,8%	189	42,2%	259	57,8%	
Missing	26	4,5%	6	23,1%	20	76,9%	
Percentage grade 3[c]			**81,5%**		**81,4%**		**p = 0.262**[b]
Resection margin -side							
Free	402	69,8%	160	39,8%	242	60,2%	
Involved (<2 mm)	71	12,3%	46	64,8%	25	35,2%	
Missing	103	17,9%	32	31,1%	71	68,9%	
Percentage involved[c]			**22,3%**		**9,4%**		**p < 0,001**[b]
Resection margin -back							
Free	490	85,1%	203	41,3%	287	58,6%	
Involved (<2 mm)	19	3,3%	10	52,6%	9	47,4%	
Missing	67	11,6%	25	37,3%	42	62,7%	
Percentage involved[c]			**4,7%**		**3,0%**		**p = 0,331**[b]
Resection margin – any							
Free	395	68,6%	158	66,4%	237	70,1%	
Involved (<2 mm)	83	14,4%	52	21,8%	31	9,2%	
Missing	98	17,0%	28	11,8%	70	20,7%	
Percentage involved[c]			**24,8%**		**11,6%**		**p < 0,001**[b]
Radiation therapy within 1 year after mastetcomy							
No	543	94,3%	216	90,8%	327	96,7%	
Yes	33		22	9,2%	11	3,3%	
Missing	0		0		0		
Percentage radiation[c]			**9,2%**		**3,3%**		**p = 0.002**[b]

[a] Student's *t*-test.
[b] Chi-square test.
[c] Missing data excluded.

4. Discussion

4.1. Main findings

Locoregional recurrence after mastectomy has historically been as low as 1–3% [11,12]. In the present study, 10-years overall recurrence was 3,0%, which is in line with previous studies. The recurrence rate was higher in the SSM than in the SM group. However, age is an important confounder, as it affects the treatment choice and the risk of death. When stratifying for the difference in age between the two groups, no statistical difference in DFS or OS was observed. Whether the higher recurrence rate among women who underwent SSM is due to the operating procedures or underlying risk factors remains unknown. SSM is a complex procedure that the elderly might not prefer. Thus, the difference in age between the two groups will probably never be balanced. We observed that lack of free resection margin in the SSM group was correlated with an increased risk of recurrence.

4.2. Mastectomy completeness

Chest wall recurrence following mastectomy for DCIS is either from the development of new cancer in residual tissue or incomplete excision of primary DCIS. A complete mastectomy is therefore essential. To remove all breast tissue and concomitantly achieve a low complication rate and good cosmetic outcomes in SSM is a challenge which needs good surgical technique and experience. The surgeons are often reluctant to perform radical removal of

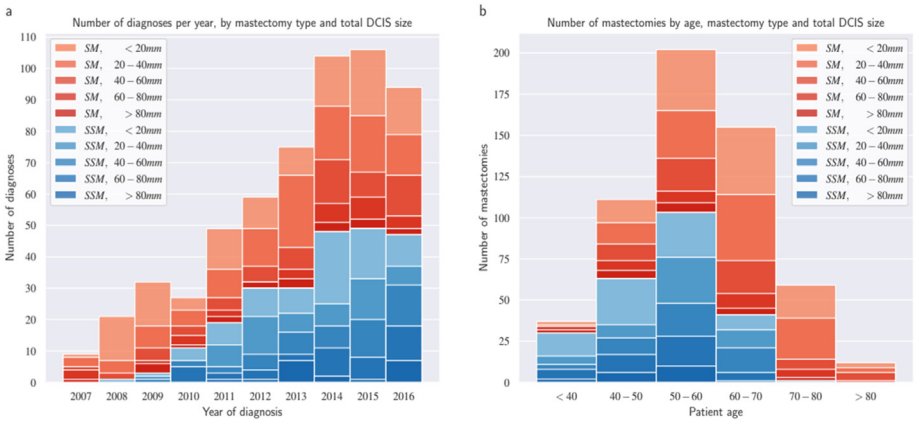

Fig. 2. Number of skin-sparing mastectomy (SSM) and simple mastectomy (SM) per year and age group by DCIS size.
2a. Increased frequencies of Skin-sparing mastectomies(SSM) in the study period, more than half of the mastectomy patients are operated with SSM in 2016.
2b. Imbalanced study population. Young patients are operated with skin-sparing mastectomy, the elderly simple mastectomy (SM).

Table 2
Time to and characteristics of the recurrences in the skin-sparing mastectomy and simple mastectomy group.

	Skin-sparing Mastectomy (n)	Simple mastectomy (n)	Total (n)
	12	3	15
Median time (months) to recurrence	32(21–86)	15(11–34)	30(11–86)
Characteristics of the primary lesion			
Median Size(mm)	65(12–100)	60(45–60)	
van Nuys' grade			
Grade1	2	0	2
Grade2	0	0	0
Grade3	10	3	13
Involved Resection margin			
Side	4	1	5
Back	2	1	3
Any	6	2	8
Radiation therapy	1	0	1
Recurrence			
Localisation			
local recurrence (LR)	9	1	10
Locoregional recurrence (LRR)	2	2	4
Nodal recurrence (NR)	1	0	1
Distant metastasis (DM)	*1*	*0*	*1*
Surgery	12	3	15
Surgical excision	12	3	15
Axillary dissection	4	2	6
Sentinel Node	3	0	3
No ax surgery	5	1	6
Infiltrating carcinomas	6	2	
Size median (mm)	14 (5–25)	7+3	
Grade1	0	NA	
Grade2	3	NA	3
Grade3	3	NA	3
Er/Her2	NA	NA	
Ki-67	45 (26–80)	62 + 18	
DCIS	6	1	7

breast tissue due to fear of complications like skin flap necrosis [23]. The breast parenchyma needs to be dissected from the covering skin at the level of the superficial fascia. Identifying this border can be difficult [24]. A few reports have indicated various amounts of residual breast tissue after SSM with a tendency to leave more at the anterior border to preserve native-skin viability [25,26]. Although the resection is performed at the superficial fascia, there might be irregular extensions into the subcutaneous tissue [24]. Torresan and colleagues evaluated residual glandular tissue after SSM, and 59,5% contained residual tissue [27] .Cao et al. reported 20% residual carcinoma in an additional biopsy over tumor [28]. This is in line with our findings of higher recurrence rates in SSM compared to SM. However, all forms of mastectomies may leave residual breast tissue. Barton et al. reported residual

Table 3
Univariate analysis of risk factors for recurrence, SSM patients (n = 238).

	HR	95% CI	P-value
Age	0,97	(0.92–1.03)	0,32
DCIS diameter	1,01	(1.00–1.03)	0,18
Number of surgeries	1,15	(0.49–2.74)	0,73
No free margin (side)	4,19	(1.03–16.98)	0,05
No free margin (back)	5,33	(1.13–25.12)	0,03
No free margin (any)	5,37	(1.51–19.18)	0,01
Radiation therapy	0,91	(0.12–7.08)	0,93

HR: Hazard ratio, CI: confidence interval, p-value: From Cox proportional hazard regression analysis. An involved surgical margin was defined as < 2 mm between DCIS and the resection margin at the sides and 0 mm against the chest wall (back). Involved margin any was defined as either involved margin back or side. Lack of free resection margins was the only significant risk factor for recurrence.

glandular tissue in 21% of radical mastectomies [29]. Thus, this cannot be the only explanation for the difference in the rate of local recurrence.

The amount of residual glandular tissue may also vary between different reconstructive approaches. In a nipple-sparing mastectomy, DCIS may be present as skip lesions [30], leaving the base of the nipple free of DCIS but with a skip lesion in the ducts in the nipple core. This might be considered when planning surgical procedures in women with widespread disease.

4.3. Resection margins and radiation therapy

A recent systematic review has demonstrated a 2-3-fold increased risk for LR with involved pathological margins after mastectomy, irrespective of post-mastectomy radiotherapy [31]. The results are in line with our findings with higher recurrences rates in the SSM group with a higher rate of involved margins and was a separate risk factor in the univariate regression analysis within SSM patients (Table 3). Challenging dissection in SSM might contribute to the high rate of involved margins in the SSM group. SSM patients might benefit from better preoperative planning and detailed information on resection margins by the pathologists to make a sound decision on the need for re-excision.

Studies on RT in patients operated with mastectomy in DCIS include few patients and are all retrospective [32,33]. Resection margin status is shown to be one of the most significant factors for recurrence in DCIS patients treated with breast-conserving surgery [33]. One could postulate that women treated with mastectomy with involved margins might benefit from RT. Post-mastectomy RT is not a standard treatment in Norway, but can be used if surgical margins are widely involved [5]. In the present study the application of RT seems to have been limited to an individualised risk. Drawing a conclusion on these small numbers with inconsequent clinical practice is impossible.

4.4. Age, grade, tumor size, and receptor status

The risk of local recurrence is also associated with factors like age, receptor status and Van Nuys grade. Adjuvant hormonal therapy also has an impact. In the present study, young women were more often operated with SSM. In the univariate Cox regression in the SSM group using age as a continuous covariate, there was no increased risk of local recurrence for younger patients (p = 0.317). Results of studies on age as an independent prognostic factor for recurrence diverge. Our results are in line with previous studies that found no statistically significant difference in the LR rate according to age [34,35]. Conversely, a recent metanalysis identified premenopausal ages and high histologic grade as a significant prognostic factor of invasive breast cancer recurrence [36]. In the present study, 13/15 women with recurrence were diagnosed with DCIS grade 3, and 50% of the recurrences were breast cancer. Our results are thus in line with the result of the recently published meta-analysis.

Norwegian guidelines do not recommend adjuvant therapy in patients treated for DCIS [5], and the Norwegian pathology reports do not ruinously include information about hormone receptor status or Her-2 status. Several large trials have investigated the role of adjuvant endocrine therapy in DCIS with significant reductions in

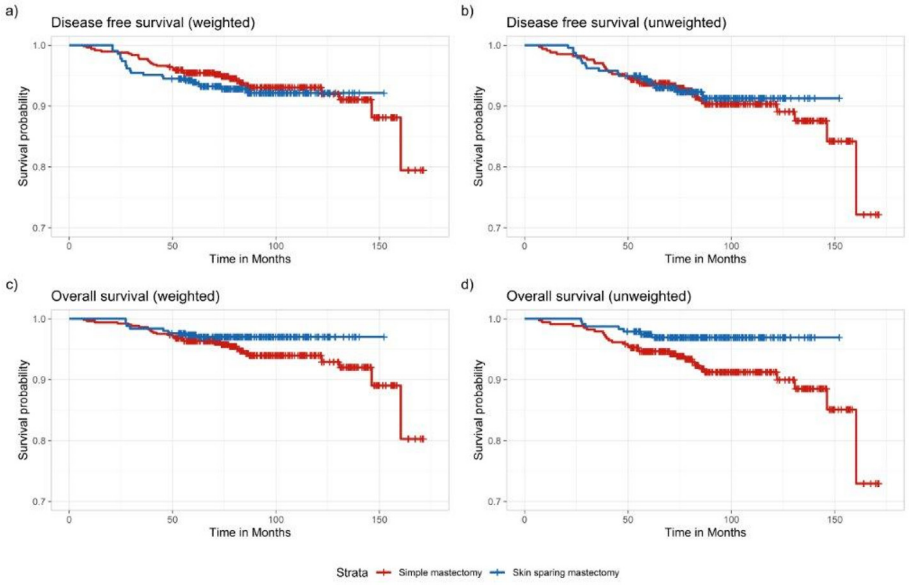

Fig. 3. a–d: Overall survival and disease-free survival with and without weighting in the skin-sparing and the simple mastectomy groups
SSM Skin-sparing mastectomies SM Simple Mastectomy. Weighted and unweighted Kaplan-Meyer plots. At ten years, the DFS in the entire population was 92.2%; 91.8% in the SSM group and 92.4% in the SM group (Fig. 3b). The overall survival in the entire population at five years was 95.0%; 97.5% in the SSM group and 93.3% in the SM group. At ten years, the OS in the entire population was 95.0%; 97.5% in the SSM group and 93.3% in the SM group (Fig. 3d). There was no significant difference in DFS or OS between the two groups when adjusting for patient age with inverse probability weighting (Fig. 3a and c).

ipsilateral recurrence and contralateral events in ER-positive disease [37,38]. Further, extensive DCIS has the potential to be underdiagnosed by pathologists. It might have foci with infiltrating disease [39]. At diagnosis, the risk of lymph node invasion in pure DCIS is less than 1% [38]. In the present study, one patient presented with isolated nodal recurrence and one with distant metastasis without local or local-regional recurrence. Both patients had extensive DCIS at primary surgery (80 mm and 90 mm). This suggests that aggressive tumor biology with microinvasion might be the explanation. Adjuvant therapy can be beneficial for some DCIS patients. Hormone receptor- and HER2 status would then be needed.

4.5. Follow-up time

The overall follow-up time was a median of 81 months (range: 7–171 months). The median time to recurrence was 30 months (range: 11–86 months). Several studies support the concept that DCIS is a long-term risk factor that will bias studies with short-term follow-up. For women treated with breast-conserving surgery, the rate almost doubles between 60 and 180 months [40]. This indicates that event rates do not drop or stabilise with time. This might be taken into consideration planning follow-up in DCIS patients.

4.6. Strengths and limitations

Our study was based on registry data, representing strengths and limitations: The completeness of data in NBCR is low. 473 patients had no information on the surgical procedure. Clinical follow-up data is scarce and based on extraction dates from the registry. However, the estimations are based on highly accurate pathology data. Other limitations are related to the retrospective study design and very few recurrences, which limit our ability to acquire substantial evidence on the risk factors. Finally, we have no information about the preservation of the nipple and secondary reconstructions, which both might influence skin excision in the SSM group.

5. Conclusions

We found a higher risk of recurrence in SSM versus SM group, and close or involved margins were correlated with an increased risk of recurrence in the SSM group. However, age was an important confounder meaning that it affects both the treatment and dead. When stratifying for the difference in age between the two groups, there was no statistical difference in DFS or OS. SSM should be preferred instead of mastectomy for patients eligible for this kind of surgery.

CRediT authorship contribution statement

Helle Kristine Skjerven: Study consept, study design, data acquisition, quality control of data algorithms, data analysis and interpretation, manuscript preparation, manuscript review writing, review and editing. **Even Moa Myklebust:** statistical analysis, quality control of data algorithms, data analysis and interpretation, manuscript preparation, manuscript review writing review and editing. **Christian Korvald:** Writing – review & editing, manuscript editing. **Alina Carmen Porojnicu:** Writing – review & editing, manuscript editing. **Rolf Kaaresen:** Writing – review & editing, manuscript editing. **Solveig Hofvind:** Writing – review & editing, manuscript editing. **Ellen Schlicting:** Writing – review & editing, manuscript editing. **Kristine Kleivi Sahlberg:** Writing – review & editing, Study concept, study design, data acquisition, quality control of data algorithms, data analysis and interpretation, manuscript preparation, manuscript editing, manuscript review.

Declaration of competing interest

The authors declare no conflict of interest.

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References

[1] Broders AC, Sr . Carcinoma of the breast (including carcinoma in situ) and its grades of malignancy and prognosis. W Va Med J 1953;49(11):311–6.
[2] Tabár L, et al. A proposal to unify the classification of breast and prostate cancers based on the anatomic site of cancer origin and on long-term patient outcome. Breast Cancer Basic Clin Res 2014;8. BCBCR.S13833.
[3] Lynge E, et al. Variation in detection of ductal carcinoma in situ during screening mammography: a survey within the International Cancer Screening Network. Eur J Cancer 2014;50(1):185–92.
[4] Cancer Registry of Norway. Annual report 2021 with results and improvements from the Norwegian breast cancer registry. Årsrapport 2021 med resultater og forbedringstiltak fra Nasjonalt kvalitetsregister for brystkreft 2022 [cited 2022; Available from: https://www.kreftregisteret.no/Generelt/Rapporter/Arsrapport-fra-kvalitetsregistrene/Arsrapport-for-brystkreft/arsrapport-for-brystkreft-2021/.
[5] Norwegian Breast Cancer Group. National guidelines for diagnosis, treatment and follow-up of breast cancer patients. Nasjonalt handlingsprogram for med retningslinjer for diagnostikk, behandling og oppfølging av brystkreft 2021 [cited 6/10/21 22/10/21]; Available from: https://www.helsedirektoratet.no/retningslinjer/brystkreft-handlingsprogram.
[6] Mannu GS, et al. Invasive breast cancer and breast cancer mortality after ductal carcinoma in situ in women attending for breast screening in England, 1988-2014: population based observational cohort study. BMJ 2020;369. m1570-m1570.
[7] Elshof LE, et al. Cause-specific mortality in a population-based cohort of 9799 women treated for ductal carcinoma in situ. Ann Surg 2018;267(5):952–8.
[8] Goodwin A, et al. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev 2013;(11):CD000563.
[9] Morrow M, et al. Society of surgical oncology-American society for radiation oncology-American society of clinical oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Ann Surg Oncol 2016;23(12):3801–10.
[10] Childs SK, et al. Impact of margin status on local recurrence after mastectomy for ductal carcinoma in situ. Int J Radiat Oncol Biol Phys 2013;85(4):948–52.
[11] Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Cancer 1999;85(3):616–28.
[12] Stuart KE, et al. Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis. BMC Cancer 2015;15:890.
[13] Campbel EJ, Romics L. Oncological safety and cosmetic outcomes in oncoplastic breast conservation surgery, a review of the best level of evidence literature. Breast Cancer 2017;9:521–30.
[14] Seth AK, Cordeiro PG. Stability of long-term outcomes in implant-based breast reconstruction: an evaluation of 12-year surgeon- and patient-reported outcomes in 3489 nonirradiated and irradiated implants. Plast Reconstr Surg 2020;146(3):474–84.
[15] Carlson GW, et al. Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. J Am Coll Surg 2007;204(5):1074–8.
[16] FitzSullivan E, et al. Incidence and consequence of close margins in patients with ductal carcinoma-in situ treated with mastectomy: is further therapy warranted? Ann Surg Oncol 2013;20(13):4103–12.
[17] Timbrell S, et al. Comparison of local recurrence after simple and skin-sparing mastectomy performed in patients with ductal carcinoma in situ. Ann Surg Oncol 2017;24(4):1071–6.
[18] Galimberti V, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. Ann Surg Oncol 2018;25(13):3849–57.
[19] Lhenaff M, et al. A single-center study on total mastectomy versus skin-sparing mastectomy in case of pure ductal carcinoma in situ of the breast. Eur J Surg Oncol 2019;45(6):950–5.
[20] Wu Z-Y, et al. Locoregional recurrence following nipple-sparing mastectomy with immediate breast reconstruction: patterns and prognostic significance. Eur J Surg Oncol 2021;47(6):1309–15.
[21] Larsen IK, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Euro J Cancer 2009;45(7):1218–31.
[22] Silverstein MJ, et al. Prognostic classification of breast ductal carcinoma-in-

situ. Lancet 1995;345(8958):1154–7.
[23] Matsen CB, et al. Skin flap necrosis after mastectomy with reconstruction: a prospective study. Ann Surg Oncol 2015;23(1):257–64.
[24] Tramm T, et al. Superficial margins in skin sparing and nipple sparing mastectomies for DCIS: a margin of potential concern. Radiother Oncol 2021;161:177–82.
[25] Papassotiropoulos B, et al. Prospective evaluation of residual breast tissue after skin- or nipple-sparing mastectomy: results of the SKINI-trial. Ann Surg Oncol 2019;26(5):1254–62.
[26] Kaidar-Person O, et al. Residual glandular breast tissue after mastectomy: a systematic review. Ann Surg Oncol 2020;27(7):2288–96.
[27] Torresan RZ, et al. Evaluation of residual glandular tissue after skin-sparing mastectomies. Ann Surg Oncol 2005;12(12):1037–44.
[28] Cao D, et al. The superficial margin of the skin-sparing mastectomy for breast carcinoma: factors predicting involvement and efficacy of additional margin sampling. Ann Surg Oncol 2008;15(5):1330–40.
[29] Barton Jr FE, et al. Glandular excision in total glandular mastectomy and modified radical mastectomy: a comparison. Plast Reconstr Surg 1991;88(3):389–92. ; discussion 393-4.
[30] Tramm T, Zuckerman K, Tavassoli FA. Skip lesion of DIN (DCIS) in the nipple in a case of breast cancer. Int J Surg Pathol 2011;19(6):817–21.
[31] Bundred J, et al. Do surgical margins matter after mastectomy? A systematic review and meta-analysis. Euro J Cancer 2020;138:S42.
[32] Chadha M, et al. Is there a role for postmastectomy radiation therapy in ductal CarcinomaIn situ? Int J Surg Oncol 2012;2012:1–5.
[33] Chan LW, et al. Is radiation indicated in patients with ductal carcinoma in situ and close or positive mastectomy margins? Int J Radiat Oncol Biol Phys 2011;80(1):25–30.
[34] Klein J, et al. Close or positive resection margins are not associated with an increased risk of chest wall recurrence in women with DCIS treated by mastectomy: a population-based analysis. SpringerPlus 2015;4(1).
[35] Carlson GWMDF, et al. Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. J Am Coll Surg 2007;204(5):1074–8.
[36] Visser LL, et al. Predictors of an invasive breast cancer recurrence after DCIS: a Systematic Review and Meta-analyses. Cancer Epidemiol Biomarkers Prev 2019;28(5):835–45.
[37] Fisher B, et al. Tamoxifen in treatment of intraductal breast cancer: national Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353(9169):1993–2000.
[38] Cuzick JP, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12(1):21–9.
[39] Silver SA, Tavassoli FA. Mammary ductal carcinoma in Situ with micro-invasion. Cancer 1998;82(12):2382–90.
[40] Shaaban AM, et al. Pathological features of 11,337 patients with primary ductal carcinoma in situ (DCIS) and subsequent events: results from the UK Sloane Project. Br J Cancer 2021;124(5):1009–17.