

Treatment of Ductal Carcinoma in situ: A Register-Based Study of Norwegian Women Diagnosed between 1995 and 2018

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Keywords

Ductal carcinoma in situ · Breast-conserving treatment · Oncoplastic surgery · Mastectomy · Surgery

Abstract

Introduction: The incidence of ductal carcinoma in situ (DCIS) has increased after implementation of mammographic screening. The lesion represents management challenges due to its undetermined growth pattern. We aimed to explore treatment of women aged 48–71 years diagnosed with DCIS between 1995 and 2018, by detection mode and histopathological characteristics. **Material and Methods:** Data on surgical treatment and radiation therapy (RT) of 4,995 women diagnosed with DCIS were retrieved from the Cancer Registry of Norway. We described the percentage and frequency of breast-conserving treatment (BCT) for participants in BreastScreen Norway (screen-detected) and nonparticipants. We estimated the relative risk (RR) of BCT, using log-binomial regression models. **Results:** Use of BCT increased from about 40% in 1995 to 85% in 2018. Use of BCT was more common among older than younger women and more commonly used for screen-detected versus tumors detected outside the screening program. Nine out of ten women with tu-

mors ≤ 10 mm were treated with BCT and two out of ten with tumors > 50 mm. RT was given to 89.3% of the women with tumors ≤ 10 mm, 34.1% of those with tumors classified as van Nuys' grade 1 and < 10 mm and 96.0% of the tumors > 50 mm. Use of BCT was less common for tumors > 50 mm compared to < 10 mm (RR adjusted for age, detection mode, van Nuys' grade, and localization: 0.26, 95% CI: 0.19–0.36). **Conclusion:** BCT was increasingly used among women diagnosed with DCIS in Norway during the period from 1995 to 2018, particularly for screen-detected, small lesions with low van Nuys' grade.

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Introduction

Ductal carcinoma in situ (DCIS) is a noninvasive precursor lesion of malignant epithelial cells within the terminal ducts of the breast [1]. DCIS displays a broad spectrum of tumor biology and the proportion of untreated DCIS that will progress to invasive breast cancer is unknown [2, 3]. However, there is a 25–30% upgrade rate from histologically verified DCIS on core biopsy to invasive ductal carcinoma at surgical excision [4]. Surgical

treatment of DCIS is therefore widely recommended [5–7]. The incidence of DCIS has increased during the last decades due to implementation of mammographic screening [8, 9] which warrants a critical evaluation of the management [10–12]. While waiting for reliable and validated markers for progression, treatment is based on tumor diameter, van Nuys' grade, comedo necrosis, localization, and the women's age [13]. Different options for surgical treatment exist, such as breast-conserving treatment (BCT) alone, BCT including radiation therapy (RT), or mastectomy and sentinel node biopsy with or without primary reconstruction. Surgical methods are continuously evolving to reduce the risk of invasive recurrence, improve the cosmetic results, and reduce side and late effects of the treatment [7, 14]. Silverstein et al. [15] found 10-year disease-free survival to be 98% for women who underwent mastectomy and 81% for those who had BCT. RT is shown to reduce the risk of recurrence of invasive tumors by approximately the half [16]. Despite having lower overall mortality, studies have shown a higher risk of dying from breast cancer among women diagnosed with DCIS compared with women in the general population with a cumulative breast cancer mortality 10 years after treatment for DCIS to be 2.3% for women <50 years of age and 1.4% for those 50 and older [17, 18].

There is an ongoing debate regarding detection and treatment of DCIS, which is argued to overdetection and overtreatment [19, 20]. Overdetection is defined as diagnosing and treatment of tumors that would not cause harm during a woman's lifetime if left untreated [21, 22]. DCIS might thus represent overdetected cases with overtreatment as a potential problem. Mastectomies in patients eligible for BCT or BCT with RT in those with low-risk DCIS are some examples. However, more knowledge is needed to offer the women optimal long-term treatment.

We took advantage of data from the Cancer Registry of Norway and explored the treatment of DCIS diagnosed in women targeted by BreastScreen Norway, stratified by detection mode. The treatment options were analyzed according to tumor diameter, van Nuys' grade, location of the tumor in the breast, age at diagnosis, and post-surgery use of RT.

Materials and Methods

This study was approved by the Data Protection Officer at the Oslo University Hospital (19/15705). We received de-identified data from the Cancer Registry of Norway, which administers BreastScreen Norway. The program invites women aged 50–69 years to two-view mammography biennially. However, due to invitation of cohorts and 2 years follow-up after the last screening exam, the age range of women screened in the program is 48–71 years, which is the age-group in our study. The recall rate was 3.8%,

while the rate of screen-detected (SD) cancer (DCIS and invasive) was 0.6%, and the interval cancer rate 0.18% in the period from 1996 to 2016. A total of 17.2% of the screen-detected and 5.9% of the interval cancers were DCIS [23].

Data about detection mode, diagnosis, treatment, and follow-up are stored in a centralized, national database at the Cancer Registry of Norway. All individuals in Norway are assigned a unique personal identification number at time of birth or immigration. This number was used to link data across databases at the registry and provide complete information for the individual woman. By law, all cancer cases are reported to the Cancer Registry of Norway, ensuring complete data capture of cancer diagnoses [24]. DCIS was systematically coded at the registry from 1996 onwards and retrospectively reviewed for cases diagnosed 1993–1995 [25]. Screen-reading, eventual further assessment, treatment, and follow-up took place at 17 breast centers, located mainly at regional or university hospitals. Since 1997, the Cancer Registry of Norway has retrieved prospectively registered data on RT on each cancer patient from all Norwegian radiotherapy centers. The unique 11-digit personal identification number enables linkage to the correct cancer cases.

Data and Variables

We received data about 5,263 women aged 48–71 years without a prior diagnosis of malignancy of the breast, diagnosed with their first DCIS, without any invasive component during the period from 1995 to 2018. We excluded data from 268 women without information about surgical treatment, leaving 4,995 women diagnosed with DCIS as the study sample (Fig. 1).

A subsample of women diagnosed between 2010 and 2018 was established to illustrate the most recent management. Information about the surgical treatment given in the pathology reports was analyzed and divided into BCT and mastectomy. BCT included surgical biopsies that removed all DCIS. If BCT was performed before mastectomy, mastectomy was used as the surgical treatment. Furthermore, we analyzed data on RT given after surgery. The women were divided into four age-groups: <55 years, 55–59 years, 60–64 years, >64 years. Detection mode was defined as SD, interval-detected (ID), and cancers detected outside the screening program (OS). In this setting, SD tumors were considered asymptomatic and ID and OS as symptomatic. A SD DCIS was diagnosed after a positive screening examination. An interval DCIS was diagnosed after a negative screening or more than 6 months after a false-positive screening and within 2 years after screening. DCIS was diagnosed among women never invited, women invited who did not attend, or those diagnosed with breast cancer more than 2 years after their last screening examination. Tumor diameter was measured on the pathology specimen and reported as a continuous variable. We grouped the tumors into the categories ≤10 mm, 11–20 mm, 21–30 mm, 31–40 mm, 41–50 mm, and >50 mm. Van Nuys' system was used for histopathological grading [23], and the localization of the lesion was reported as lower lateral, lower medial, upper lateral, upper medial and central quadrant.

All women treated with BCT in the subsample (diagnosed 2010–2018) were described for each category of the independent variables (age, detection mode, DCIS diameter, van Nuys' grade, and localization), in addition to the proportions of women who received hypofractionated RT (40.2 Gy in total, 2.67 Gy for 5 days a week for 3 weeks). Further, we analyzed the association between RT and DCIS diameter (≤10 mm, 11–20 mm, and >20 mm) and van Nuys' grade. We then used log-binomial regression models to estimate the relative risk (RR) of BCT. We hypothesized that the surgical decision process involved the consideration of the interaction between the clinical size of the DCIS and its location in addition to van Nuys' grade, i.e., that a small DCIS would have a differ-

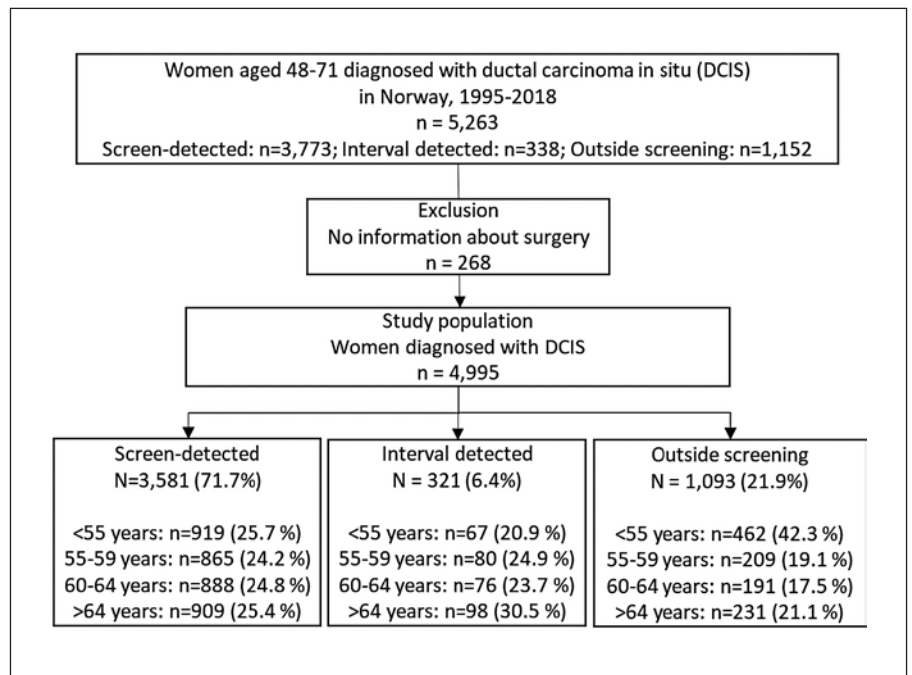


Fig. 1. Study sample.

ent RR of BCT depending on its location within the breast. However, when using the tumor diameter given by the pathologist post-surgery, none of these two interaction terms proved a meaningful predictor of surgical technique in the regression model and additionally increased the information criteria, indicating a less parsimonious model. Our final model thus included crude and adjusted RRs according to age, location, diameter, and van Nuys' grade. The interaction between the variables was illustrated graphically. All data management and analysis were performed using Stata MP 16.1 (College Station, TX, USA).

Results

We included 4,995 women who received surgical treatment for DCIS (shown in Fig. 1). Of those, 3,581 (71.7%) were SD, 321 (6.4%) ID, and 1,093 (21.9%) were detected outside the screening program. Mean ages were 59.6 years for SD DCIS, 60.5 years for ID, and 57.6 years for those detected outside the screening program. Further characteristics of the 2,404 women and the tumor diagnosed during the period 2010–2018 are summarized in Table 1. The proportion of BCT increased during the study period for all detection modes from 37.8% (17/45) in 1996 to 84.5% (202/239) in 2018 for SD and from 31.1% (14/45) to 74.5% (38/51) for those detected due to symptoms, outside the screening program (Fig. 2).

In recent years, 2010–2018, 72.5% (1,742/2,404) of all women diagnosed with DCIS were treated with BCT, varying by detection mode; 75.3% (1,391/1,848) for SD, 65.2% (118/181) for ID, and 62.1% (233/375) for those outside the screening program (Table 1). Women aged <55 years had the lowest proportion of BCT of 64.7% (410/634), while

women >64 years had the highest (76.2%, 509/668). Women with tumor diameter ≤ 10 mm were more often treated with BCT (88.9%, 511/575) compared to those with tumor diameter >50 mm (19.9%, 37/186). Use of BCT decreased by van Nuys' grading of the tumor and by the combination of tumor diameter and grading (Table 1).

More than half of the DCIS were in the upper lateral quadrant (55%, 1,054/1,916). DCIS located in the upper medial quadrant of the breast had the highest percentage of BCT (81.6%, 231/283), while the lowest percentage was found for lesions located in the lower medial quadrant (67.6%, 144/213) (Table 1). Women with DCIS 30 mm or smaller were more often treated with BCT compared to women with tumors larger than 40 mm, regardless of localization (Fig. 3).

RR_{adj} for BCT decreased by increasing tumor diameter (RR_{adj} : 0.97 [95% CI: 0.92–1.03, $p = 0.31$] for DCIS 11–20 mm and RR_{adj} : 0.26 [95% CI: 0.19–0.36, $p < 0.001$] for tumors >50 mm), using <10 mm as the reference. DCIS of higher van Nuys' grade were less likely to be treated with BCT than van Nuys' grade 1 (RR_{adj} : 0.84 [95% CI: 0.77–0.91, $p < 0.001$] for van Nuys' grade 2 and RR_{adj} : 0.83 [95% CI: 0.77–0.89, $p < 0.001$] for van Nuys' grade 3). The log-binomial regression models showed a statistically significant association of age on the risk of BCT for women with DCIS. The association remained stable after adjusting for detection mode, location, tumor diameter, and van Nuys' grade (RR_{adj} : 1.14, 95% CI: 1.06–1.23, $p = 0.001$) for women aged 60–64 years when using those aged <55 years as reference (Table 2).

Information about RT was available for 1,058 of the 1,135 (93.2%) women who underwent BCT during the

Table 1. Number of women diagnosed with DCIS and treated with breast cancer surgery, percentage BCT, and percentage of women registered with RT in Norway, 2010–2018

	Information on surgery available, <i>n</i>	BCT		Information on RT available, <i>n</i> *	Treatment with RT	
		<i>n</i>	%		<i>n</i>	%
DCIS cases	2,404	1,742	72.5	1,135	1,058	93.2
Detection mode						
SD	1,848	1,391	75.3	953	887	93.1
ID	181	118	65.2	65	62	95.4
Outside screening	375	233	62.1	117	109	93.2
Age						
<55 years	634	410	64.7	252	230	91.3
55–59 years	513	376	73.3	251	236	94.0
60–64 years	589	447	75.9	302	287	95.0
>64 years	668	509	76.2	330	305	92.4
DCIS diameter						
≤10 mm	575	511	88.9	319	285	89.3
11–20 mm	628	522	83.1	411	399	97.1
21–30 mm	371	256	69.0	197	191	97.0
31–40 mm	203	115	56.7	89	87	97.8
41–50 mm	122	35	28.7	22	20	90.9
>50 mm	186	37	19.9	25	24	96.0
Information not available	319	266		72	52	
van Nuys' grade						
1	361	324	89.8	136	94	69.1
2	257	203	79.0	146	142	97.3
3	1,614	1,057	65.5	817	799	97.8
Information not available	172	158		36	23	
Localization of the tumor						
Lower lateral quadrant	236	173	73.3	122	116	95.1
Lower medial quadrant	213	144	67.6	100	95	95.0
Upper lateral quadrant	1,054	782	74.2	528	492	93.2
Upper medial quadrant	283	231	81.6	145	136	93.8
Central	130	103	79.2	68	63	92.6
Information not available	488	309		172	156	

* Information about RT was not available for 607/1,742 women treated with BCT.

period from 2010 to 2018 (Table 1). A total of 89.3% (285/319) with DCIS ≤10 mm had RT, while it was 96.0% (24/25) of those with tumors >50 mm. While 69.1% (94/136) with DCIS van Nuys' grade 1 had RT, 97.8% (799/817) of those with van Nuys' grade 3 underwent such therapy. When combining diameter and van Nuys' grade, we found women with tumors <10 mm and grade 1 to be treated with RT in 34.1% (15/44), while it was 98.1% (53/54) of the women with the same diameter but grade 2 and 98.6% (214/217) for grade 3 (Table 3).

Discussion/Conclusion

In this register-based cohort study of about 5,000 women aged 48–71 years diagnosed with DCIS, the proportion of BCT increased from about 40% in 1995 to 85% in 2018. BCT was more commonly used among women

with SD tumors, those with small tumor diameter, low van Nuys' grade, and among those aged 55 years or older. We identified use of RT in 34% of the women with DCIS <10 mm and van Nuys' grade 1.

BCT is associated with good cosmetic outcomes, shorter hospital stays, and better quality of life over time compared to mastectomy [26]. This is important to communicate to the women. However, communication of evidence-based information may be influenced by the health care personnel providing the information. A study from the US showed that women informed by a radiation oncologist or a breast surgeon more often choose BCT than those informed by a general surgeon [27]. Breast and endocrine surgery became a surgical subspecialty in Norway 2008. This, together with the implementation of BreastScreen Norway during the period from 1996 to 2005, the number of hospitals involved in breast diagnostics, and treatment, was reduced from 64 to about 20 [28,

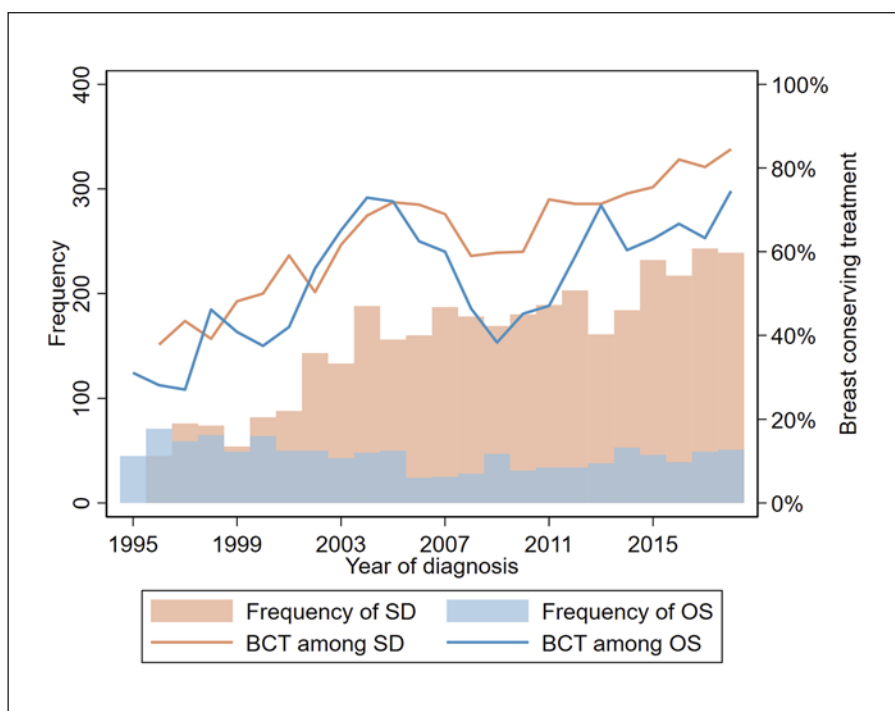


Fig. 2. Timeline of the proportion of BCT versus mastectomy for women diagnosed with DCIS in Norway 1995–2018.

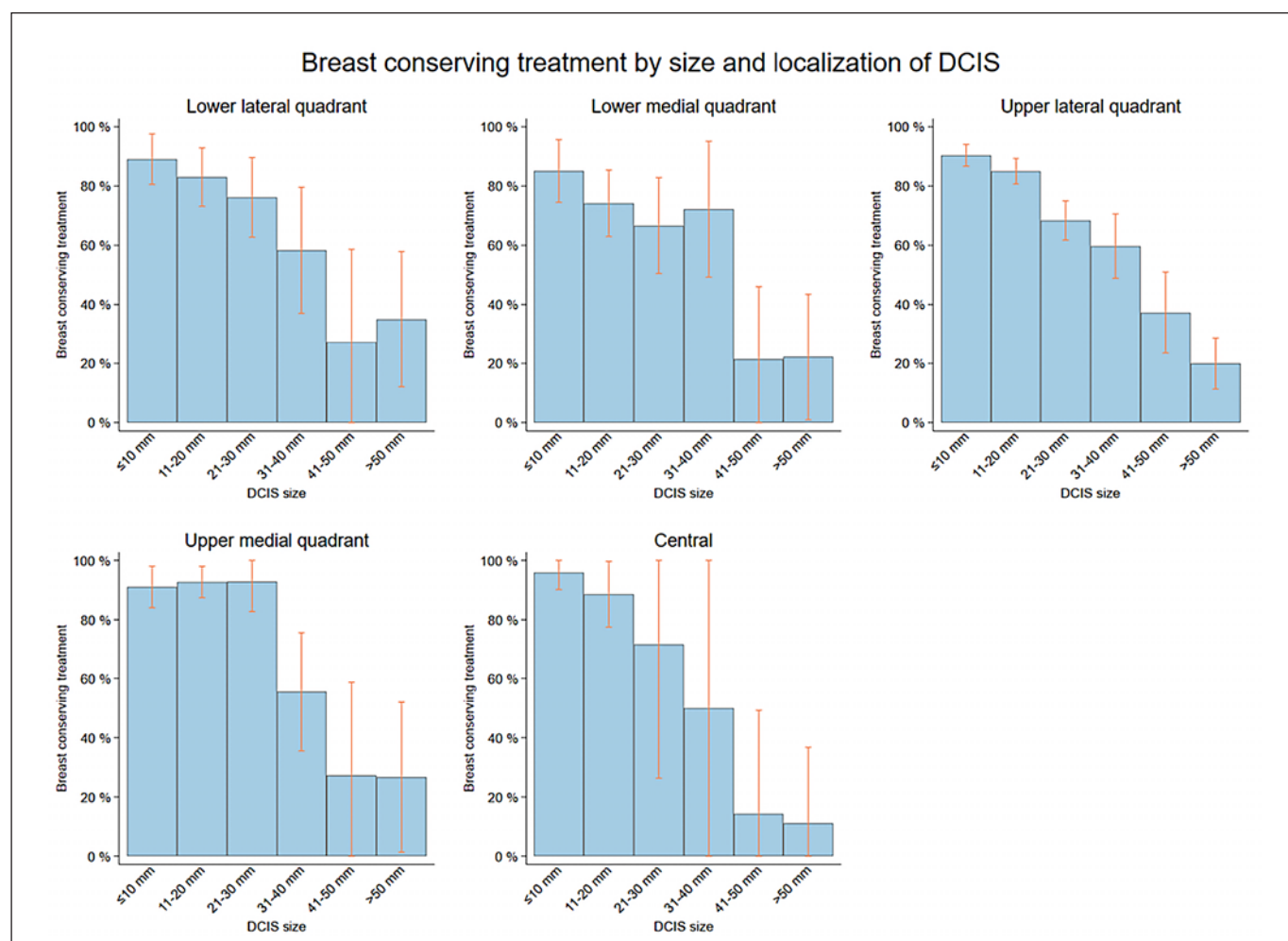


Fig. 3. Breast conserving treatment by size and localization of ductal carcinoma in situ (DCIS).

Table 2. RR of BCT among DCIS patients in Norway with reported lesion characteristics (*n* = 1,677) 2010–2018

	RR for BCT					
	crude RR	95% CI	<i>p</i> value	adjusted RR	95% CI	<i>p</i> value
Age at diagnosis						
<55 years	1.00	–	–	1.00	–	–
55–59 years	1.13	1.03–1.24	0.01	1.14	1.06–1.23	0.001
60–64 years	1.18	1.08–1.29	<0.001	1.16	1.07–1.25	<0.001
>64 years	1.15	1.05–1.26	0.002	1.07	1.00–1.15	0.06
Detection mode						
SD	1.00	–	–	1.00	–	–
ID	0.92	0.77–1.10	0.34	1.14	1.00–1.31	0.05
Outside screening	0.81	0.67–0.98	0.03	0.89	0.74–1.05	0.17
DCIS diameter						
≤10 mm	1.00	–	–	1.00	–	–
11–20 mm	0.94	0.90–0.98	0.009	0.97	0.92–1.03	0.31
21–30 mm	0.78	0.72–0.85	<0.001	0.82	0.75–0.88	<0.001
31–40 mm	0.66	0.58–0.75	<0.001	0.67	0.59–0.77	<0.001
41–50 mm	0.34	0.25–0.46	<0.001	0.36	0.26–0.48	<0.001
>50 mm	0.25	0.18–0.34	<0.001	0.26	0.19–0.36	<0.001
DCIS localization						
Lower lateral quadrant	1.00	–	–	1.00	–	–
Lower medial quadrant	0.92	0.80–1.04	0.18	0.94	0.85–1.04	0.25
Upper lateral quadrant	0.99	0.90–1.09	0.85	1.10	0.95–1.08	0.74
Upper medial quadrant	1.12	1.01–1.24	0.04	0.97	0.89–1.06	0.47
Central	1.07	0.95–1.22	0.27	0.98	0.89–1.08	0.73
Van Nuys' grade						
1	1.00	–	–	1.00	–	–
2	0.86	0.79–0.93	<0.001	0.84	0.77–0.91	<0.001
3	0.74	0.70–0.77	<0.001	0.83	0.77–0.89	<0.001

29]. This might be of influence for the increased use of BCT during the study period.

Current publications have suggested a major risk of deformity after standard BCT when more than 20% of the breast volume is excised and as little as 5% when the location of the malignancy is in the lower medial quadrant [30, 31]. Our findings support breast cancer surgery in line with these statements as we found lower rates of BCT with increased tumor diameter and when tumor was in the lower medial quadrant of the breast. However, increased use of oncoplastic breast surgery techniques by the breast and plastic surgeons allow immediate remodeling of large resection defects even in lower quadrants with wide margins [32]. The increased use of BCT among women with tumors located in the lower quadrants as well as when the tumor diameter exceeded 50 mm in our subpopulation aligns with the introduction of oncoplastic surgery in Norway recent years.

Until 2005, the Norwegian national guidelines did not recommend BCT for DCIS larger than 40 mm. Further, the resection margin was reduced from 5 to 2 mm in 2008 [6, 7, 33]. Closer margins might result in a reduction of excised breast volume. These changes in guidelines have opened for an increased use of BCT. Currently, mastec-

tomy is only indicated for women with extensive or multicentric DCIS, a high family genetic risk, or when the breast volume related to the lesion diameter compromises the achievement of clear margins with a favorable cosmetic outcome.

There was a temporary decline in BCT for DCIS during the period from 2005 to 2009. This decline has also been reported in other studies, for DCIS and for invasive breast cancer [29, 34, 35]. The trend could be attributed to the interpretation of the Early Breast Cancer Trialists' Group review published in 2005 which suggested an increased incidence of local recurrences and a higher breast cancer mortality in women treated with BCT [36]. Later studies disproved these findings [34], after which the rates of BCT has increased steadily [29]. In our study, 84.5% of women diagnosed with DCIS had BCT in 2018, which is close to the European Society of Breast Cancer Specialists (EUSOMA) target of 90% for noninvasive breast cancer smaller than 20 mm [14]. However, a further increase in use of BCT might be possible.

We found BCT to be most used among women aged >55 years, increasing by age. This is in line with a prior study on surgical treatment of breast cancer in Norway 2003–2018 [32]. Studies have shown an association be-

Table 3. Number and percentage of women diagnosed with ductal carcinoma in situ and who underwent RT after BCT by tumor diameter and van Nuys' grade ($n = 1,677$), Norway, 2010–2018

DCIS diameter – van Nuys' grade	BCT	RT	
	<i>N</i>	<i>n</i>	%
≤10 mm – van Nuys' grade 1	44	15	34.1
≤10 mm – van Nuys' grade 2	54	53	98.1
≤10 mm – van Nuys' grade 3	217	214	98.6
11–20 mm – van Nuys' grade 1	54	49	90.7
11–20 mm – van Nuys' grade 2	39	38	97.4
11–20 mm – van Nuys' grade 3	316	311	98.4
21–30 mm – van Nuys' grade 1	24	23	95.8
21–30 mm – van Nuys' grade 2	45	44	97.8
21–30 mm – van Nuys' grade 3	258	250	96.9
Information not available	36	23	63.9

tween younger age at diagnosis and an increased risk for adverse outcomes [37, 38].

Some have hypothesized that mastectomy is chosen by patients for more expedient treatment to avoid RT [39]. The introduction of hypofractionated radiotherapy in Norway in 2010, with a reduction from 5 to 3 weeks of RT might be less stressful, especially among those living far away from the radiation facility, and thus contributed to the increased use of BCT. Even shorter RT is now recommended [40]. However, this procedure is not yet implemented in Norway [7].

Factors associated with RT in our study were lesions' diameter and van Nuys' grade; large lesion diameter and high grade associated with higher risk of recurrence, suggesting that health care providers involved in the management of DCIS have selected women for RT based on factors associated with higher risk of recurrence [16, 41, 42]. However, the difficulty remains in identifying the subgroup of women in whom the absolute benefit of treatment of DCIS may be small. When combining DCIS diameter and van Nuys' grade, we found lesions <10 mm and grade 1, which is assumed to be low-risk lesions, to be treated with RT in as much as 34.1% of the patients. This is not in line with national or international guidelines [5–7] and might represent overtreatment. Prospective trials among women with low-risk DCIS treated with BCT have demonstrated lower rates of local recurrence compared with previous results from randomized controlled trials [43].

The diagnosis and management of DCIS is highly complex. All DCIS may not become invasive or will recur. Further knowledge about biology and growth is needed to separate which DCIS will progress or not to further refine patient selection for treatment. Studies have demonstrated that the molecular profile of DCIS lesions is highly predictive of recurrence [44–46]. Future treatment

might be grounded on evidence from these studies as well as ongoing studies comparing surgery versus watchful waiting/observation in women with low-risk DCIS: the surgery versus active monitoring for low-risk DCIS (LORIS) trial [47], the low-risk DCIS (LORD) trial [48], and the Comparison of Operative to Monitoring and Endocrine Therapy (COMET) [49].

Our study was based on registry data with a high level of accuracy and completeness, which represent a strength. However, the study also has limitations. We had no information about multifocality or multicentricity, gene mutation status, or breast volume that may affect treatment decision-making. As most of all DCIS cases were diagnosed within the screening program, the study population was restricted to women aged 48–71 years. Further, survival analyses were not included in this study. Death due to DCIS is very uncommon, and survival analyses of women with this disease require a substantial number of women diagnosed and treated for the disease and followed for several years to get valid results. In addition, several other factors will be of importance to include in such analyses; recurrence and new cancer in the ipsi- and contralateral breast, comorbidity, etc. These topics are extensive and will be presented in a separate paper. Finally, despite the uncertainty about the origin and nomenclature of DCIS, we chose to use the term DCIS in this manuscript [50].

In conclusion, the surgical management of DCIS has changed during the last two decades in Norway, with an increased use of BCT. Implementation of breast oncoplastic with precision surgery together with the change in the treatment recommendations are probably the main reasons. Further knowledge about DCIS and risk of recurrence is needed to further personalize the treatment of the disease and reduce overtreatment.

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Statement of Ethics

This research project complies with the guidelines for human studies according to the Declaration of Helsinki as revised in 2013. The Cancer Registry Regulation waived the requirement to obtain written informed consent for this retrospective analysis of anonymized data from BreastScreen Norway; institutional review board approval is not required. The study was recommended by the Data Protection Officer at the Oslo University Hospital (19/15705). Ethical approval was thus not required. We received de-identified data from the Cancer Registry of Norway, which administers BreastScreen Norway.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study concept and design were contributed by Solveig Hofvind, Helle Skjerven, and Anders Skyrud Danielsen. Data were acquired by Solveig Hofvind and Anders Skyrud Danielsen. Quality control and analysis of data were conducted by Solveig Hofvind and Anders Skyrud Danielsen. The manuscript was prepared by Helle

Skjerven and Anders Skyrud Danielsen. All the authors helped draft the work, revised it critically for important intellectual content, and read and approved the final version to be published. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Data can be made available provided that the processing is in accordance with the principles set out in Article 5 of the General Data Protection Regulation (GDPR) and has legal basis in Articles 6 (1) (e) and 9 (2) (j) of the GDPR. In addition, the processing must have supplementary basis in Union or Member State law and ethical approval from the Regional Committees for Medical and Health Research Ethics. The data can only be made available to a third country or an international organization, subject to the other provisions of GDPR, the conditions laid down in Chapter V is complied with.

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