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A low risk of recurrence after breast-conserving surgery for DCIS: A single-institution experience

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ABSTRACT

Background: : Previously published studies report up to 30% recurrence rates after DCIS, so it would be desirable to identify those women at risk for recurrence and adapt adjuvant management. This study aimed to identify the locoregional recurrence rate after breast conserving surgery (BCS) for DCIS, and to evaluate the possible role of immunohistochemical (IHC) staining in predicting the risk of recurrence.

Patients and methods: : In a retrospective cohort study, patients who underwent BCS for pure DCIS were identified. Data on well-established clinical-pathological risk factors and development of locoregional recurrence was gathered from patient files. In addition, IHC stains of ER, PR, HER2, p53, and ki67 were performed on original tumor samples. Univariable Cox regression analyses were performed to identify possible risk factors for locoregional recurrence.

Results: : 190 patients were included. At a median follow-up time of 12.8 years fifteen (8%) patients developed locoregional recurrence: 7 invasive cancer and 8 DCIS. These recurrences were diagnosed within a range of 1.7 to 19.6 years after the initial diagnosis. Univariable Cox regression analysis did only show a significant association between p53 and locoregional recurrence. Our re-excision rate to obtain free margins was 30.5%, and 90% received radiotherapy. Endocrine treatment was not used.

Conclusions: : At 12.8 years follow-up, patients with DCIS treated with BCS have a very low locoregional recurrence of 8%. Although we could demonstrate that increased p53 expression is a risk factor for locoregional recurrence, we think this is of little clinical value in our population with such a low recurrence rate.

Microabstract: : With a published recurrence rate up to 30% after DCIS, it would be desirable to identify those at risk to adapt treatment and follow-up. We aimed to evaluate the role of immunohistochemical staining to determine the risk of locoregional recurrence, in addition to established clinical and pathological risk factors. At a median follow-up of 12.8 years, we found a locoregional recurrence rate of 8%. Increased expression of p53 is associated with an increased risk of locoregional recurrence.

Introduction

In the management of ductal carcinoma in situ (DCIS), surgical excision has been the standard of care in the Netherlands [1,2]. Previously published studies report up to 30% locoregional recurrence rates with widely diverging follow-up times ranging from 19 months till more than 15 years [3–7]. Several prognostic factors are known for the risk of locoregional recurrence in patients with DCIS. These include age at diagnosis, initial presentation, breast density, nuclear grade, tumor size, surgical margins, and adjuvant therapy [7–9].

In the management of invasive breast cancer, biological tumor characteristics have a well-established importance in risk assessment and choice of endocrine therapy and chemotherapy [1,10–12]. The importance of biomarkers is also shown in studies on immunotherapy in the management of breast cancer. [13–15] However, in the management of DCIS, the role of biomarkers is not well established yet [3,16].

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With a locoregional recurrence rate up to 30%, it would be desirable to identify those women at risk for locoregional recurrence and adapt adjuvant treatment and follow-up. In a systematic review, Lari and Kuerer (2011) showed the potential of biomarkers in DCIS as a prognostic factor for locoregional recurrence. In this extensive overview four out of sixteen studies showed an association between ER-negative DCIS and local recurrence. The presence of PR-negative DCIS was significantly correlated with recurrence in two out of thirteen studies, and a significant correlation between HER2 positivity and disease recurrence was shown in four out of fifteen studies. Nevertheless, the studies in this systematic review were limited by small numbers of patients, variability in the extent of surgery, use of endocrine and radiation therapy, and immunohistochemical staining [3].

Although there seems to be a potential for biomarkers to estimate the risk of locoregional recurrence after breast conserving surgery (BCS) for DCIS, data to predict this risk of recurrence are inconclusive. Therefore, this study aimed to identify the locoregional recurrence rate after BCS for pure DCIS in daily clinical practice, and to evaluate the possible role of commonly available biomarkers in the risk assessment of these recurrences.

Methods

Study design

The study was a retrospective analysis of patients who received BCS in the management of DCIS in the period between January 2000 and December 2013 at the Albert Schweitzer hospital in Dordrecht, the Netherlands. Our institutional review board approved the study.

Patient selection

Patients who presented at our hospital had been referred by their general practitioner for breast related symptoms or by the national screening program. The Dutch breast cancer screening program consists of biennial mammographic screening. Every woman between the age of 50 and 75 years receives an invitation to participate in this program. In case suspect lesions are detected on mammography, patients are referred to a hospital for further analysis.

Each patient received the standard diagnostic work-up for suspect breast lesions. This work-up consists of physical examination, radiologic imaging (digital mammography, ultrasound examination of the breast and axilla), and biopsy. All breast lesions were discussed in a multidisciplinary consultation. Based on radiographic characteristics and the size of the breast itself, the patient and the treating physician chose for mastectomy or BCS with adjuvant radiotherapy. Following the Dutch breast cancer guidelines, endocrine therapy does not have to be advised as adjuvant treatment of DCIS. Follow-up consisted of annual mammography, up to at least five years after treatment [1].

In this study, patients were included if they had received BCS in the management of DCIS. Patients were excluded in case the surgical specimen showed invasive carcinoma.

Patients were also excluded when based on multidisciplinary consultation it was advised that an additional mastectomy needed to be performed within three months after the initial surgery, due to positive resection margins in relation to the size of the breast.

All biopsies and surgical specimen were reviewed by a pathologist to confirm the diagnosis of DCIS. Patient-related variables were gathered from electronic medical records of our institutional database.

Follow-up

Locoregional recurrence was defined as recurrence of DCIS or invasive breast cancer in the ipsilateral breast, axilla or regional lymph nodes. All events were identified, and the interval between the primary treatment and locoregional recurrence was recorded.

The follow-up time was defined as the time between the primary diagnosis of DCIS until March 2023. In case of a locoregional recurrence, the date of locoregional recurrence was used as last follow-up date. When a mastectomy was performed for other reasons than locoregional recurrence, the date of surgery was used as last follow-up date. In case a patient was deceased, the date of death was as last date of follow-up. For patients that might have been treated at another hospital, a linkage with PALGA (the national registry of histopathology and cytopathology) was established and all available data was added to our dataset in case of missing variables.

The imaging follow-up was defined as the time between the primary diagnosis until the last imaging of the breast performed in our hospital.

Immunohistochemical stains

Immunohistochemical (IHC) stains of ER, PR, HER2, p53 and ki67 were performed. These biomarkers were chosen based on their well-established function as prognostic factor and these are the most often used biomarkers in the management of invasive breast cancer [3,11,12,17]. IHC was performed on the biopsy samples. In case biopsy material did not contain enough material for staining, IHC was performed on the surgical specimen. All additional staining was reviewed by an experienced breast pathologist. Based on review of the literature, we used a cut-off of 10% for p53 [9,18] and 20% for Ki67 [19–21].

Data analysis

Patient demographics and biopsy variables were analyzed using descriptive analyses, presented as means with standard deviation or numbers with percentages. Univariable Cox regression analyses were performed to identify possible risk factors for the development of locoregional recurrence. The predictors in the univariable Cox regression analyses were age (at diagnosis), DCIS grade, ER status, ~~and~~ HER2 status, p53 and ki67. The incidence of developing locoregional recurrence after BCS for pure DCIS was presented in a Kaplan-Meier curve. In case of missing data, complete case analyses were performed. Two-sided p-values of < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS version 24.

Results

Patient population

In total, 190 patients with DCIS who received BCS in the period between January 2000 and December 2013 were identified. Of these patients, 158 (83%) patients had screen-detected DCIS and 29 (15%) patients had clinical breast symptoms. Of the patients who presented with clinical symptoms, the majority (17 out of 29 patients) presented with palpable mass. The median age at first presentation was 58 years (Table 1).

Histopathology

Of the 190 patients, 32 (17%) patients had a radiologic-discordant finding or another reason than biopsy-proven DCIS to proceed to BCS. In seven (4%) cases the histopathological result of the biopsy was suspicious of invasive carcinoma. This suspicion of invasive carcinoma was not confirmed in the surgical specimen. The median tumor size was 13 mm. 16 (8%) patients had comedonecrosis in the surgical specimen. In the final diagnosis, 37 (19%) patients had DCIS grade 1, 58 (31%) patients had DCIS grade 2, and 95 (50%) patients had DCIS grade 3. ER was positive in 147 (77%) patients, PR was positive in 111 (58%) patients, and HER2 was positive in 45 (24%) patients. In 138 (73%) patients p53 was $\leq$ 10%, and ki67 was $\leq$ 20% in 172 (91%) patients (Table 1).

Table 1
Patient demographics of 190 patients who received BCS in the management of DCIS.

	Number of patients (n)	Percentage (%)	
Median age at first presentation [minimum – maximum], *, in years	190		58.0 [26, 79] IQR: 14
Menopausal status			
Pre-menopausal	7	3.7	
Peri-menopausal	10	5.3	
Post-menopausal	44	23.2	
Unknown	129	67.9	
Initial presentation			
Screen	158	83.2	
Clinical	29	15.3	
Missing	3	1.6	
Symptoms (in case of clinical presentation)	17	8.9	
Palpable mass	3	1.6	
Nipple discharge	2	1.1	
Changes skin or nipple	7	3.7	
Other			
Palpable lesion at side of DCIS			
No	157	82.6	
Yes	18	9.5	
Not noted	15	7.9	
Side of DCIS			
Left	97	51.1	
Right	92	48.4	
missing	1	0.5	
BI-RADS mammography			
BI-RADS 1	2	1.1	
BI-RADS 2	2	1.1	
BI-RADS 3	19	10.0	
BI-RADS 4	149	78.4	
BI-RADS 5	11	5.8	
Missing	7	3.7	
Histopathological result biopsy			
DCIS grade 1	30	15.8	
DCIS grade 2	54	28.4	
DCIS grade 3	69	36.3	
Other	32	16.8	
Missing	5	2.6	
Histopathological result biopsy with suspicion for invasive disease	158	83.2	
No	7	3.7	
Yes	25	13.2	
Missing			
Comedonecrosis in surgical specimen	161	84.7	
No	16	8.4	
Yes	13	6.8	
Missing			
Median size tumor [minimum – maximum], *, in mm	138		13 [1, 61] IQR: 14
Estrogen receptor status			
Negative	35	18.4	
Positive	147	77.4	
Missing	8	4.2	
Progesterone receptor status			
Negative	64	33.7	
Positive	111	58.4	
Missing	15	7.9	
Her2/neu receptor status			
Negative	126	66.3	
Positive	45	23.7	
Missing	19	10.0	
P53 status			
≤ 10%	138	72.6	
> 10%	38	20.0	
Missing	14	7.4	
Ki67 status			
≤ 20%	172	90.5	
> 20%	3	1.6	
Missing	15	7.9	
DCIS grade**			
DCIS grade 1	37	19.5	
DCIS grade 2	58	30.5	
DCIS grade 3	95	50.0	
Surgical margins after primary surgery	110	57.9	
Free	54	28.4	
Focal	25	13.2	
Positive			
***Re*-operation**			
No	132	69.5	
Yes	58	30.5	
Definitive surgical margins (after re-operation)	174	91.6	
Free	13	6,8	
Focal	3	1.6	
Positive			
Adjuvant radiotherapy			
No, due to medical reasons	6	3.2	
No, at patients request	5	2.6	
Yes	171	90.0	
Missing	8	4.7	
Median follow-up time [minimum – maximum], *, in years	190		12.8 [1.0 – 22.8] IQR: 5.8
Median time to last imaging [minimum – maximum], *, in years	184		10.0 [0.9 – 19.6] IQR: 2.0
Imaging during follow-up			
Not performed	6	3.2	
Mammography	182	95.8	
MRI	1	0.5	
Ultrasound	1	0.5	
BI-RADS at last imaging during follow-up	3	1.6	
BI-RADS 1	166	87.4	
BI-RADS 2	6	3.2	
BI-RADS 3	5	2.6	
BI-RADS 4	4	2.1	
BI-RADS 5			
Development of breast cancer ***			
No	151	79.5	
Yes, ipsilateral	11	5.8	
Yes, contralateral	24	12.6	
Yes, both sides	4	2.1	
Median time to locoregional recurrence [minimum – maximum], IQR*, in years	15		9.1 [1.7 – 19.6] IQR: 8.75

* IQR = interquartile range
** Highest DCIS grade diagnosis in biopsy and surgical specimen
*** invasive carcinoma and/or ductal carcinoma in situ.

Surgery & surgical margins

The histopathologic results of the primary surgery showed free surgical margins in 110 (58%) patients, focally positive margins, or narrow margins in 54 (28%) patients, and positive surgical margins in 25 (13%) patients. Nine (5%) patients had multiple excisions during the primary surgery. Only one of these nine patients had narrow margins and received adjuvant radiotherapy with boost instead of a re-operation. Not all patients with involved margins opted for re-operation. Of the 79

patients with involved margins, 58 (73%) patients underwent a breast conserving re-operation. After re-operation(s) two patients still had focally positive margins, and one patient had positive surgical margins. Two of these patients received adjuvant radiotherapy, and one patient did not opt for adjuvant radiotherapy due to her comorbidities (Table 1). Endocrine therapy was not used as adjuvant treatment.

Follow-up & locoregional recurrence

During a median follow-up time of 12.8 years, a new breast cancer event in the ipsilateral breast was diagnosed in eleven patients. A new breast cancer event in the contralateral breast was diagnosed in twenty-four patients, and in four patient breast cancer manifested in both breasts. During the follow-up time twenty-four patients died (13%) after a median time of 10.3 years after their diagnosis. In two cases this was breast cancer related. In both cases the DCIS samples were revised, but no signs for invasive disease were found.

Fifteen (8%) patients developed locoregional recurrence, and this manifested in a range of 1.7 to 19.6 years after initial diagnosis. The estimated cumulative five-year incidence is 0.027 (Fig. 1). The histopathologic diagnosis of locoregional recurrence was pure DCIS in eight patients, invasive carcinoma in six patients, and one patient had a combination of invasive carcinoma and DCIS (See Table 2 for more details).

The univariable Cox regression analyses for locoregional recurrence showed a significant association with p53 ($p = 0.037$) and did not show a significant association with age at diagnosis ($p = 0.654$), DCIS grade ($p = 0.757$), ER status ($p = 0.484$), or HER2 status ($p = 0.631$) (Table 3).

Discussion

After more than 10 years of follow-up, patients who received BCS for DCIS have a very low risk of locoregional recurrence. Only fifteen (8%) patients developed an ipsilateral event, eight of which consisted of DCIS and seven invasive carcinomas. There was only a significant association between p53 and locoregional recurrence, but there was no significant association between the risk of locoregional recurrence and age at diagnosis, DCIS grade, ER status, HER2 status, and ki67. The locoregional recurrence rate was lower than the contralateral breast cancer event rate of 15% in thirteen years. In the Netherlands the incidence rate of DCIS in the general population is approximately 13% of all breast cancer events per year (2300/18,000 breast cancer events per year) [22].

Previously published data report a risk of locoregional recurrence for DCIS up to 30% [3–7]. We found a very low locoregional recurrence rate of 5% at ten years. This is even lower than the 7.1% recurrence rate that was recently reported in a Dutch multi-center study [2]. In the Netherlands, the breast cancer guideline recommends to pursue free surgical margins. This policy results in a low threshold for re-excision. In the regional multidisciplinary consultation at our institute, re-excision for (focal) positive surgical margins was chosen over radiation therapy with boost. So, in the current study, the re-operation was 31%. In case of re-excision, this study only included patients who received a second BCS, and patients who received mastectomy after BCS were not included in this study. Our re-excision rate is high compared to the average re-excision rate of approximately 14% in the Netherlands [23], and also higher than the re-excision rate of 23% found in the study of Jobsen et al. [2]

Previous studies reported invasive breast cancer in approximately 50% of recurrences [3]. Although we only found fifteen locoregional recurrences, our results (eight DCIS, and seven invasive carcinomas) seem comparable with the existing literature [3].

In our study, ER, PR, HER2, p53 and ki67 were chosen based on their well-established function as prognostic factor, and most often used in the management of invasive breast cancer. We found that patients with an increased expression of p53 in DCIS are at an increased risk of locoregional recurrence with a hazard rate of three, but with a wide confidence interval and we did not correct for multiple testing. We did not find an association between the other immunohistochemical biomarkers and locoregional recurrence. Kerlikowske et al. (2010), found several biomarkers that could identify women with an increased risk for breast recurrence after DCIS. In a cohort with a recurrence rate of 28%, they showed that the recurrence rate was higher in case of p16, COX2, and ki67 triple positive DCIS [18]. In an extensive review, Lari and

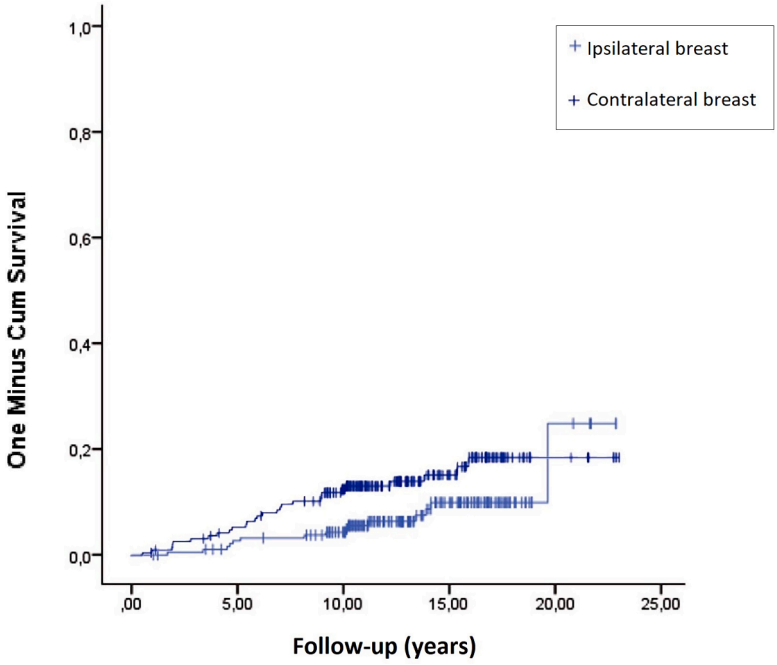

Fig. 1. . Kaplan Meier curve
One minus the cumulative incidence of the development of breast cancer in the ipsilateral breast compared to the development of breast cancer in the contralateral breast.

Table 2
Patient characteristics of **15** patients with locoregional recurrence.

Patient	Age at primary diagnosis	DCIS grade	Location primary DCIS	Tumor size (mm)	ER status	PR status	HER2 status	P53 status	Ki67 status	Surgical margins	Adjuvant radiotherapy	Time to recurrence, in years	Location recurrence	Histopathologic result recurrence
1	52	3	Right, UOQ	40	+	–	–	<10%	<20%	Free	Yes	4.76	Right, UOQ	DCIS
2	51	2	Left, central	15	+	+	–	<10%	<20%	Free after re-operation	Yes	4.48	Left, central	DCIS
3	53	3	Right, LIQ	13	+	+	–	>10%	<20%	Free after re-operation	Yes	5.11	Right, LOQ	Invasive carcinoma
4	57	2	Left, UOQ	3	n/a *	n/a *	n/a *	n/a *	n/a *	Free	Yes	9.14	Left, UOQ	DCIS
5	67	2	Right, LIQ	n/a	+	+	–	<10%	<20%	Focal	Yes	11.14	Right, Central	DCIS
6	74	2	Left, UOQ	n/a	+	+	–	>10%	<20%	Free after re-operation	Yes	3.35	Left, LOQ	Invasive carcinoma
7	55	1	Left, Central	n/a	+	–	–	<10%	<20%	Free after re-operation	n/a	10.07	Left, Central	DCIS
8	41	3	Right, UOQ	25	–	–	+	>10%	<20%	Free after re-operation	Yes	4.62	Right, Central	DCIS
9	52	3	Right, LIQ	30	–	–	+	>10%	<20%	Free after re-operation	Yes + boost	14.11	Right, LIQ	DCIS + invasive carcinoma
10	50	3	Right, UOQ	30	–	–	+	<10%	<20%	Focal	Yes	1.67	Right, Central/UOQ	DCIS
11**	63	3	Left, Central	27	+	+	–	<10%	<20%	Free after re-operation	Yes	10.17	Left, Central-lateral	Invasive carcinoma + DCIS
12	58	3	Right, Central	n/a	–	–	+	<10%	<20%	Free	Yes	19.62	Right, UIQ	Invasive carcinoma
13	51	3	Left, UOQ	**12**	+	–	+	>10%	<20%	Free	Yes	8.1	Left, LOQ	Invasive carcinoma
14	**57**	3	Right, UOQ	19	+	+	–	<10%	**<**20%	Free after re-operation	Yes	13.86	Right UIQ	DCIS
15	79	1	Left, LOQ	n/a	+	+	–	>10%	<20%	Positive	No, at patients request	13.37	Left, LOQ	Invasive carcinoma

*Lesion too small for immunohistochemical staining.
**At the time of recurrence, presentation with breast cancer in both breasts.

Table 3
Univariable Cox regression analyses for locoregional recurrence.

	n	hazard ratio	95% CI (hazard ratio)	p-value
Age (at diagnosis)	190	0.987	0.933 – 1.044	0.654
DCIS grade				0.757
Grade 1	37	0.618	0.133 – 2.867	0.539
Grade 2	58	0.716	0.220 – 2.324	0.578
Grade 3	95	*	*	*
ER status				
Negative	35	1.521	0.470 – 4.917	0.484
Positive	147	*	*	*
Her2 status				
Negative	126	0.631	0.252 – 2.305	0.631
Positive	45	*	*	*
p53 status				
Negative	138	0.313	0.105 – 0.932	0.037
Positive	38	*	*	*
Ki67 status**	175	1.002	0.917 – 1.095	0.963

* reference group.
** **tested as continues variable due to limited number of positive (>20%) cases.**

Kuerer (2011) confirmed the potential of biomarkers in DCIS and the risk of breast cancer recurrence. However, they also showed the inconsistency in studies and stated that it has not been adequately studied in DCIS [3]. Visser et al. (2019) published a systematic review and meta-analysis on predictors of invasive breast cancer recurrence after DCIS. They found six prognostic factors associated with invasive recurrence (African-America race, premenopausal status, detection by palpation, involved margins, high histologic grade, and high p16 expression). No significant association was found between recurrence and ER, PR, HER2, p53, or ki67 expression [24]. Recently, Akrida and Mulita (2023) showed the clinical significance of pre-operative HER2 expression and the risk of ipsilateral breast cancer recurrence [25].

This study is limited by its retrospective design which may introduce bias. Selection bias might also be introduced due to selection of patient's primary treated with breast conserving surgery. It is also important to be aware of our heterogeneous patient population, as all patients treated at our institute with pure DCIS were included. Nevertheless, this resulted in a true representation of our patient population in clinical daily practice. Second, the cut-off for surgical margins was not consistent over the years, and not unambiguously mentioned in the pathology reports. Nevertheless, we used the conclusion in the pathology reports because adjuvant management was based on this conclusion.

The lack of proven biomarkers for locoregional recurrence of DCIS is usually attributed to limited sample size, the diversity of markers that have been tested, differences in methodology by which the markers are tested, and the lack of confirmatory studies. We attempted to do a confirmatory study for several promising widely used biomarkers; due to a low locoregional recurrence rate, the power of our study was limited, and we were only able to confirm an increased expression of p53 as a risk factor for locoregional recurrence. Nevertheless, the size of our study is in line with studies with positive findings concerning the predictive power of several biomarkers, however the main difference is the low locoregional recurrence rate in our study. [9,18,26,27] We find it also noteworthy, that in our study the locoregional recurrence rate is lower than the incidence of contralateral breast cancer, mitigating the clinical need for additional biomarkers. This does not mean that biomarkers could not be of clinical utility. Nowadays, active surveillance is considered as an alternative to surgery, for low-risk DCIS and several studies are underway. To discriminate between low- and high-grade DCIS, ER- and HER2 status are often determined [28]. Also in the current Dutch active surveillance study for low grade DCIS (LORD), ER- and HER2-status are used: DCIS with Her2 positivity and/or ER negativity is excluded from the study. [29] The role of biomarkers is also studied in patients with DCIS treated with BCS to select those in which radiotherapy may be omitted [30]. There even is a prospective randomized trial (NSABP B-43) that studied the use of Trastuzumab concurrent to adjuvant radiotherapy in high-risk HER2 positive DCIS, and they showed that this therapy results in a reduction of ipsilateral breast cancer recurrence rates. Although, this finding was not statistically significant, it does show the potential of biomarkers in patients with DCIS [25,31]. De-escalation and personalization in the management of DCIS will be the main focus for future studies.

Conclusion

At thirteen years follow-up, patients with DCIS treated with BCS and radiotherapy have a very low locoregional recurrence rate of 8% which is probably the result of good adherence to treatment guidelines, such as re-excision and adjuvant radiotherapy. Based on a locoregional recurrence rate this low, the clinical use of predictive biomarkers for locoregional recurrence seems to be limited. However, in de-escalation and personalization of treatment for DCIS, biomarkers could play a role in the future.

CRediT authorship contribution statement

Sara van Bekkum: Data curation, Formal analysis, Writing – original draft. **Caroline Drukker:** Data curation, Formal analysis, Writing – review & editing. **Joost van Rosmalen:** Methodology, Validation, Writing – review & editing. **Marian B.E. Menke-Pluijmers:** Conceptualization, Supervision, Validation, Writing – review & editing. **Pieter J. Westenend:** Conceptualization, Supervision, Writing – review & editing.

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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References

[1] Dutch breast cancer guideline (2021). Available at: https://richtlijnendatabase.nl/richtlijn/borstkanker.
[2] J.J. Jobsen, L.J.E.E. Scheijmans, W.G.J.M. Smit, M.C. Stenfert Kroese, H. Struikmans, J. van der Palen, Breast-conserving therapy for primary Ductal Carcinoma in Situ in The Netherlands: a multi-center study and population-based analysis, Breast 42 (2018) 3–09.
[3] S.A. Lari, H.M. Kuerer, Biological markers in DCIS and risk of breast recurrence: a systematic review, J. Cancer 2 (2011) 232–261.
[4] M. van Seijen, E.H. Lips, A.M. Thompson, et al., Ductal carcinoma in situ: to treat or not to treat, that is the question, Br. J. Cancer 121 (2019) 285–292.
[5] I.L. Wapnir, J.J. Dignam, B. Fisher, et al., Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS, J. Natl. Cancer Inst. 103 (2011) 478–488.
[6] N. Bijker, P. Meijnen, J.L. Peterse, et al., Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of european organisation for research and treatment of cancer randomized phase III trial 10853 - A study by the EORTC breast cancer cooperative group an, J. Clin. Oncol. 24 (21) (2006) 3381–3387.
[7] J. Boyages, G. Delaney, R. Taylor, Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis, Cancer 85 (3) (1999).
[8] J.M.B. Pang, K.L. Gorringe, S.B. Fox, Ductal carcinoma in situ - update on risk assessment and management, Histopathology 68 (2016) 96–109.
[9] E. Rakovitch, S. Nofech-Mozes, W. Hanna, et al., HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ, Br. J. Cancer 106 (2012) 1160–1165.
[10] K. Mokbel, B. Cutuli, Heterogeneity of ductal carcinoma in situ and its effects on management, Lancet Oncol. 7 (2006) 756–765.
[11] O. Abe, R. Abe, K. Enomoto, et al., Tamoxifen for early breast cancer: an overview of the randomised trials, Lancet 351 (9114) (1998).

[12] A. Schramm, N. De Gregorio, P. Widschwendter, V. Fink, J Huober, Targeted therapies in HER2-positive breast cancer - a systematic review, Breast Care 10 (3) (2015).
[13] G. Viscardi, A.C. Tralongo, F. Massari, et al., Comparative assessment of early mortality risk upon immune checkpoint inhibitors alone or in combination with other agents across solid malignancies: a systematic review and meta-analysis, Eur. J. Cancer 177 (2022) 175–185.
[14] A. Rizzo, A. Cusmai, S. Acquafredda, L. Rinaldi, G. Palmiotti, Ladiratuzumab vedotin for metastatic triple negative cancer: preliminary results, key challenges, and clinical potential, Expert Opin. Investig. Drugs 31 (6) (2022).
[15] A. Rizzo, A.D. Ricci, Biomarkers for breast cancer immunotherapy: PD-L1, TILs, and beyond, Expert Opin. Investig. Drugs 31 (6) (2022).
[16] L. Salvatorelli, L. Puzzo, G.M. Vecchio, R. Caltabiano, V. Virzì, G. Magro, Ductal carcinoma in situ of the breast: an update with emphasis on radiological and morphological features as predictive prognostic factors, Cancers (Basel) 12 (609) (2020) 1–11.
[17] A. Nordenskjöld, H. Fohlin, T. Fornander, B. Löfdahl, L. Skoog, O. Stål, Progesterone receptor positivity is a predictor of long-term benefit from adjuvant tamoxifen treatment of estrogen receptor positive breast cancer, Breast Cancer Res. Treat. 160 (2) (2016).
[18] K. Kerlikowske, A.M. Molinaro, M.L. Gauthier, et al., Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis, J. Natl. Cancer Inst. 102 (2010) 627–637.
[19] R. Tashima, R. Nishimura, T. Osako, et al., Evaluation of an optimal cut-off point for the Ki-67 index as a prognostic factor in primary breast cancer: a retrospective study, PLoS ONE 10 (7) (2015).
[20] A. Lombardi, R. Lazzeroni, L. Bersigotti, V. Vitale, C. Amanti, The proper Ki-67 cut-off in hormone responsive breast cancer: a monoinstitutional analysis with long-term follow-up, Breast Cancer Targets Ther. 13 (2021).
[21] L.P. Feeley, A.M. Mulligan, D. Pinnaduwage, S.B. Bull, I.L. Andrulis, Distinguishing luminal breast cancer subtypes by Ki67, progesterone receptor or TP53 status provides prognostic information, Mod. Pathol. 27 (4) (2014).
[22] Integraal Kankercentrum Nederland (IKNL), NKR cijfers, Selection: survival, invasive breast cancer. 2011-2017, (2023). Available at: https://iknl.nl/kankersoorten/borstkanker/registratie/incidentie.
[23] B. Schermers, Y.E. van Riet, R.J. Schipper, et al., Nationwide registry study on trends in localization techniques and reoperation rates in non-palpable ductal carcinoma in situ and invasive breast cancer, Br. J. Surg. (2021).
[24] L.L. Visser, E.J. Groen, F.E. Van Leeuwen, E.H. Lips, M.K. Schmidt, J. Wesseling, Predictors of an invasive breast cancer recurrence after DCIS: a Systematic Review and Meta-analyses, Cancer Epidemiol. Biomarkers Prev. 28 (5) (2019).
[25] I. Akrida, F. Mulita, The clinical significance of HER2 expression in DCIS, Med. Oncol. 40 (1) (2023) 1–18.
[26] J.Y. Kim, K. Park, G. Kang, H.J. Kim, G. Gwak, Y.J. Shin, Predictors of recurrent ductal carcinoma in situ after breast-conserving surgery, J. Breast Cancer 19 (2) (2016).
[27] K. Han, S. Nofech-Mozes, S. Narod, et al., Expression of HER2neu in ductal carcinoma in situ is associated with local recurrence, Clin. Oncol. 24 (3) (2012).
[28] M.R. Van Bockstal, M.C. Agahozo, L.B. Koppert, C.H.M. van Deurzen, A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast, Int. J. Cancer 146 (5) (2020).
[29] L.E. Elshof, K. Tryfonidis, L. Slaets, et al., Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study, Eur. J. Cancer 51 (2015) 1497–1510.
[30] C.A. Knowlton, R.B. Jimenez, M.S. Moran, Risk assessment in the molecular era, Semin. Radiat. Oncol. 32 (3) (2022).
[31] K.P. Siziopikou, S.J. Anderson, M.A. Cobleigh, et al., Preliminary results of centralized HER2 testing in ductal carcinoma in situ (DCIS): NSABP B-43, Breast Cancer Res. Treat. 142 (2) (2013).