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Original article

Breast-conserving therapy for primary Ductal Carcinoma in Situ in The Netherlands: A multi-center study and population-based analysis

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ABSTRACT

Objective: The aim of this study was to analyse the efficacy of breast-conserving therapy (BCT) for women with primary DCIS in a population-based setting.
Methods: Data were used from five Radiotherapy centres in The Netherlands from 2000 to 2010, all treated with BCT. Of all the cases, 59.2% received a boost of radiotherapy after their whole breast irradiation (WBI), irrespective of margin status.
Results: A total of 1248 cases with primary DCIS were analysed. The 10-years LRFS was 92.9%. Age $\leq$50 years and a positive margin were significantly related to local relapse free survival (LRFS). Having a boost had no impact on LRFS, showing a nearly equal recurrence pattern in patients with and without a boost. Separate analyses were done on patients who had received and not received a boost of radiotherapy after WBI. We noted 9.1% contra-lateral breast tumours. The 10-years disease specific survival (DSS) rate was 99.0%.
Conclusions: DCIS of the breast and treated with BCT results in excellent LRFS and DSS. Primary surgical lumpectomy with negative margins followed by WBI seems to be the treatment of choice in DCIS treated with BCS with respect to IBTR.

1. Introduction

Ductal Carcinoma in Situ (DCIS) is not considered to be an invasive carcinoma (IC), but a premalignant lesion. It displays a broad spectrum of tumour biology. Traditionally, DCIS has been treated through breast conserving surgery (BCS) or ablative surgery. Nationwide screening mammography was initiated in The Netherlands in 1990. From 1990 until 2016,we noted an increase of DCIS in The Netherlands from 375 to 2675 cases per year. Furthermore, a sharp increase in the incidence of DCIS was noted after 2005 [1,2].

In the 1980s and 1990s, four randomized controlled trials were performed to evaluate the efficacy of whole breast irradiation (WBI) following BCS in women with DCIS [3–7]. In a recent review, Shah et al. concluded from these results that surgery and WBI should remain the standard care treatment in the management of DCIS [8].

However, over the past decade, doubt has emerged as to whether current treatment paradigms for DCIS may represent overtreatment. In 2015, Narod et al. presented the results of an observational study of more than 100.000 women diagnosed with DCIS, finding the 20-year rate of breast cancer mortality to be 3.3% [9]. Invasive cancer recurrences represent about 50% of all recurrences and are associated with a low rate of breast cancer mortality [4,6,7].

The addition of WBI is associated with long-term side effects. In 2012, the long-term cosmetic changes after breast-conserving

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therapy (BCT) of 348 breast cancer participants of the EORTC 'boost versus no boost' trial showed that a boost dose worsened the breast appearance the during the initial years and that the development of fibrosis associated with WBI is an ongoing process [10]. Considering cardiovascular morbidity and mortality, a recent study noted no increased risk, with 10-year median follow-up, after radiotherapy for DCIS when compared with surgery alone [11].

In The Netherlands, since the first results of the EORTC 10853 trial, BCT has been the standard treatment for localized DCIS [6]. This trial, together with two other trials, resulted in roughly a 35%–45% reduction in local recurrence with WBI. However, in contrast to invasive breast cancer the survival benefit for adjuvant WBI has not been established with DCIS. However, in a recent large longitudinal cohort study reported by Sagara et al. (n = 32.144, SEER-data) the prognostic score of DCIS (Smith et al.) identifies subgroups of patients for whom the breast cancer mortality and overall mortality will decrease by applying WBI. In another analysis of SEER data (Qian 2015, n = 56.968) WBI had showed a survival benefit for patients ≤ 50 years and negative ER-status [12–14]. Further studies will be needed to confirm these findings. Internationally there is a growing interest in omitting WBI for low risk patients or administrating partial breast radiotherapy. Therefore, it is important to also assess the efficacy of DCIS treatment (including WBI) in a population-based setting.

This study aims to assess the efficacy of BCT for women with primary DCIS in a population-based setting.

2. Patients and methods

Clinical data from 1328 patients with DCIS and all treated between 2000 and 2011 through BCT, were collected from five radiotherapy departments in The Netherlands. In the Netherlands,

Table 1
Patients and tumour characteristics of 1248 patients with ductal carcinoma in situ (DCIS) and treated through breast-conserving therapy.

Characteristics	All Patients n = 1248 (%)	No-boost group n = 509 (%)	Boost group n = 739 (%)	P value
Age				
≤51 years	244 (19.5)	102 (20.0)	142 (19.2)	
>50 years	1004 (80.4)	407 (80.0)	597 (80.8)	ns
Family history on first degree relative				
None	884 (70.8)	366 (71.9)	518 (70.1)	
One first degree relative	233 (18.7)	90 (17.7)	143 (19.3)	ns
≥2 first degree relatives	53 (4.2)	24 (4.7)	29 (3.9)	
Unknown	78 (6.2)	29 (5.7)	49 (6.6)	
Localisation primary				
Lateral upper quadrant	644 (51.6)	266 (52.3)	378 (51.1)	
Lateral lower quadrant	107 (8.6)	53 (10.4)	54 (7.3)	
Medial upper quadrant	196 (15.7)	83 (16.3)	113 (15.3)	ns
Medial lower quadrant	87 (7.0)	31 (6.1)	56 (7.6)	
Central	192 (1534)	65 (12.8)	127 (17.2)	
Unknown	22 (1.8)	11 (2.2)	11 (1.5)	
Primary surgery				
Lumpectomy	586 (47.0)	276 (54.2)	310 (41.9)	
Lumpectomy + re-excision	235 (18.8)	109 (21.4)	126 (17.1)	<0.001
Lumpectomy + re-excision + SN	51 (4.1)	3 (0.6)	48 (6.5)	
Lumpectomy + SN (axilla)	374 (30.0)	120 (23.6)	254 (34.4)	
Unknown	2 (0.2)	1 (0.2)	1 (0.1)	
Histology				
Ductal carcinoma in situ	1219 (97.7)	495 (97.2)	724 (98.0)	
Intracyst. papillary carcinoma	22 (1.8)	9 (1.8)	13 (1.8)	ns
Morbus Paget	7 (0.6)	5 (1.0)	2 (0.3)	
Malignancy grading				
Grade 1	190 (15.2)	134 (26.3)	56 (7.6)	
Grade 2	445 (35.7)	187 (36.7)	258 (34.9)	<0.001
Grade 3	559 (44.8)	157 (30.8)	402 (54.4)	
Unknown	54 (4.3)	31 (6.1)	23 (3.1)	
Margin Status				
Negative	970 (77.7)	443 (87.0)	527 (71.3)	
Positive	73 (5.8)	13 (2.5)	60 (8.1)	<0.001
Marginal ≤1 mm	193 (15.5)	47 (9.2)	146 (19.8)	
Unknown	12 (1.0)	6 (1.2)	6 (0.8)	
Tumour size				
<11 mm	385 (30.8)	165 (32.4)	220 (29.8)	
11–20 mm	417 (33.4)	174 (34.2)	243 (32.9)	ns
>20 mm	164 (13.1)	65 (12.8)	99 (13.4)	
Unknown	282 (22.6)	105 (20.6)	177 (23.9)	
Low Risk DCIS				
None	1149 (92.1)	433 (85.1)	716 (96.9)	<0.001
Yes	99 (7.9)	76 (14.9)	23 (3.1)	
Timing radiotherapy after lumpectomy				
<36 days	453 (36.3)	132 (25.9)	321 (43.4)	
36–56 days	509 (40.8)	213 (41.8)	296 (40.1)	<0.001
>56 days	286 (22.9)	164 (32.2)	122 (16.5)	
Histology contra lateral tumour				
None	1135 (90.9)	461 (90.6)	674 (91.2)	
DCIS	34 (2.7)	13 (2.5)	21 (2.8)	ns
Invasive carcinoma	79 (6.3)	35 (6.9)	44 (5.9)	

P-value has been calculated on the known components of the variables.

the incidence of DCIS over the period between 2000 till and 2010 averaged about 1500 per year [2]. About half of those were treated through BCT, so about 7500 cases. This cohort represents about 20% of the nationwide DCIS cases treated through BCT.

The patients were reviewed for the following factors: age at diagnosis, the presence of a first degree family history (FH) of breast cancer, date of the lumpectomy, histology, malignancy grading, margin status, start of WBI, and follow-up data including the date of ipsilateral breast tumour recurrence (IBRT), contra-lateral breast tumour (CBT), and patient's status at last follow-up. For two patients, no follow-up data were available. To be included in this population-based study, the minimum follow-up period had to be more than one year. We also excluded those patients with a history of breast tumour, DCIS or invasive carcinoma (IC) in the contra-lateral breast, ultimately resulting in 1248 patients for analyses.

Of all patients, 97.7% were pure DCIS (Table 1) and showed no evidence of invasive disease or node involvement. IBRT included both invasive carcinoma (IC) and DCIS in the ipsilateral breast.

A positive resection margin was defined as showing the presence of DCIS at the inked margin. A marginal free resection margin was defined as indicating the presence of DCIS at a distance of $\leq$1 mm from the inked margin. FH was defined as the history of the first-degree relatives (FDR) suffering from breast cancer. CBT was defined as a breast tumour (IC or DCIS) in the contra-lateral breast. We defined a synchronous bilateral breast tumour (SBBT) as a breast tumour diagnosed in both breasts simultaneously within three months of the first tumour. Metachronous bilateral breast tumour (MBBT) was defined as a breast tumour occurring in the contra-lateral breast more than three months after diagnosis of the first breast that was affected.

2.1. Treatment

BCT was defined as lumpectomy followed by whole breast irradiation (WBI) with or without a boost dose directed to the primary tumour area. In some cases the lumpectomy was accompanied by an axillary dissection and after the introduction of the sentinel lymph node procedure (SN) with a SN. In the case of a positive margin status, a re-excision was usually carried out. The WBI regime consisted of 50 Gy, delivered in 2 Gy fractions five times a week, or an equivalent scheme. In case of a boost, this could be administered after the WBI (sequential) or as a simultaneous integrated boost (SIB) irradiation. The radiotherapy regime, with respect to the WBI and the boost, depended on the guidelines of each particular institution and changed over time. Table 2 shows the various types of primary surgery and the radiotherapy regimes used.

No adjuvant endocrine therapy was used during the study period.

2.2. Statistical methods

Time to recurrence and length of follow-up were calculated from the start of the (first) lumpectomy. To test between-group differences for categorical data, the Chi-square test was used.

The local recurrence-free survival (LRFS) is defined by survival time without IBTR.

For survival analyses, patients were censored if they had not experienced an event (IBTR) by the date of last follow up or by the date of death.

For comparison of survival distributions, the Log Rank test was used. Univariate analysis was performed on all known histological, treatment, time and age-related variables.

The Cox proportional hazards model was used to test for the independent effect after adjusting for known prognostic factors, and hazard ratios (HR) at 95% confidence intervals (CI) are presented. Variables that were univariatly related to the outcomes of interest ($p < 0.05$) were included in the multivariate analyses. For the two different boost groups, those variables with the above-mentioned criteria in one of the groups were included in the multivariate analysis.

Table 2
Radiotherapy characteristics of 1248 breast-conserving treatments.

Characteristics	BCT n (%)
Radiotherapy	
WBI	509 (40.8)
WBI + SIB boost	294 (23.6)
WBI + Sequential Boost	445 (35.7)
Different Radiotherapy schemes of WBI ± boost	
WBI 4256 (16 fractions)	30 (2.4)
WBI 4730 (22 fractions)	6 (0.5)
WBI 44/45/4600 (20/15/23 fractions)	3 (0.2)
WBI 5000 (25 fractions)	470 (37.7)
SIB 4620 + 966 (22 fractions)	43 (3.4)
SIB 4715 + 1403 (23 fractions)	4 (0.3)
SIB 5040 + 1400 (28 fractions)	81 (6.5)
SIB 5068 + 1372 (28 fractions)	134 (10.7)
SIB 5104 + 1711 (29 fractions)	13 (1.0)
SIB 5146 + 2232 (31 fractions)	19 (1.5)
Seq. 4256 + 1330 (21 fractions)	19 (1.5)
Seq. 4730 + 1720 (30 fractions)	30 (2.4)
Seq. 5000 + 14/16000 (32/33 fractions)	350 (28.0)
Seq. 5000 + 20/26000 (35/38 fractions)	46 (3.7)

WBI: whole breast irradiation; SIB: simultaneous integrated boost; Seq.: sequential boost.

The timing of RT was defined by the number of days from lumpectomy until the start of radiotherapy, and was used as a separate variable in the analyses. In categorizing the various time-intervals, we took into consideration the NBCA indicator and the literature [11–13]. Patients were categorized into three time-intervals with respect to the timing of RT: <36 days, 36–56 days, and >56 days.

We created a variable low-risk DCIS, and defined it as: patients with malignancy grade one, negative margin, aged more than 45 years, no family history of breast cancer, no SBBT [15,16]. We also used the patients' prognostic score as modified by Smith et al., and shown in Fig. 1 [13].

All analyses were performed using STATA 14.2 (Stata Press, College Station, TX, USA; Stata Corporation)

3. Results

The follow-up periods for all patients ranged from 13 to 210 months with a median of 91 months. Tumour and treatment characteristics are shown in Tables 1 and 2

3.1. Ipsilateral breast tumour recurrence (IBTR)

The IBTR rate for all patients was 6.0% (75/1248). Of those 75 patients, 46.7% suffered a DCIS recurrence, 38.7% suffered IC, and 14.7% suffered DCIS + IC recurrence. The localisation of the recurrence was in 33.3% of cases in the primary tumour area, in 30.7% in the same quadrant, in 28.0% in the rest of the ipsilateral breast, and in 8.0% of the cases the location was unknown.

The 10-year LRFS was 92.9%. In multivariate Cox regression analysis, age $\leq$50-years (HR 2.2), a positive margin (HR 2.8), and a tumour size >20 mm (HR 2.0) were all significantly associated with a worse LRFS; see Table 4. Having had a boost or not did not shown significance in the multivariate analysis.

Points	Age (years)	Tumour size (mm)	Histology	Score
0	>60	<16	Low grade	0
1	40 – 60	16 – 40	Intermediate grade	↓
2	<40	>40	High grade	6

Fig. 1. Patient Prognostic Score; risk stratification. Modified from Smith et al.

3.2. IBTR by boost status

Fig. 2 shows the IBTR-estimates according to boost status, showing a nearly equal recurrence pattern for both boost status.

Table 3 shows the univariate analyses results for the various tumour and treatment characteristics according to boost or no-boost. None of the variables showed significance for either group. Cases with a positive margin and no-boost did worse compared to those with a negative margin. For the boost group, a positive margin did not show a significantly worse LRFS compared to a negative margin.

Separate analyses for the various boost techniques, such as

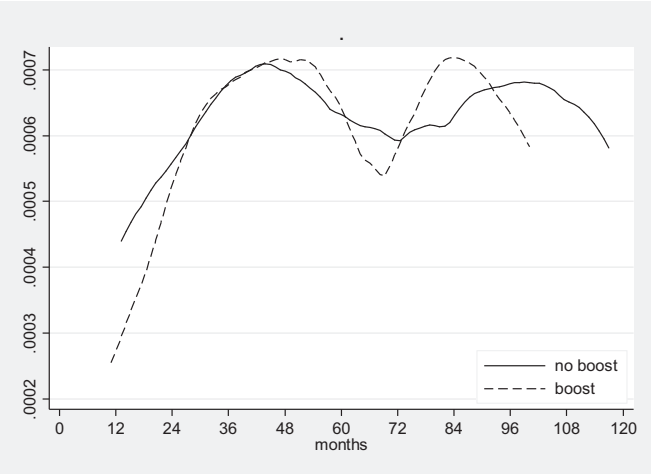

Fig. 2. The 10-years IBTR estimates for 1248 patients with ductal carcinoma in situ and treated through breast-conserving therapy according to boost or no-boost after whole breast irradiation.

Table 3
Univariate analyses Hazard Rate (HR) and confidence interval of ipsilateral breast tumour recurrence on local relapse free survival according to boost radiotherapy.

Characteristics	No-boost group HR (95% CI)	P value	Boost group HR (95% CI)	P value
Age				
≤51 years	1		1	
>50 years	0.5 (0.2–1.2)	0.119	0.4 (0.2–0.7)	**0.004**
Family history on first degree relative				
None	1		1	
≥1 first degree relatives	0.9 (0.4–2.3)	0.872	1.3 (0.6–2.8)	0.514
Unknown	2.8 (0.9–8.1)	0.062	1.4 (0.3–5.9)	0.656
Localisation primary				
Lateral upper quadrant	1		1	
Lateral lower quadrant	0.6 (0.1–2.8)	0.543	2.1 (0.6–7.6)	0.247
Medial upper quadrant	1.3 (0.5–3.4)	0.575	2.3 (0.9–6.0)	0.080
Medial lower quadrant	1.3 (0.3–5.8)	0.705	1.8 (0.5–6.7)	0.341
Central	0.9 (0.2–3.0)	0.836	2.5 (1.0–6.1)	**0.037**
Unknown	4.9 (1.0–21.6)	0.036	n a	
Re-excision				
None	1		1	
Yes	1.4 (0.7–3.2)	0.349	2.5 (1.2–4.9)	**0.009**
Malignancy grading				
Grade 1	1		1	
Grade 2	1.6 (0.6–4.6)	0.357	0.7 (0.2–2.5)	0.575
Grade 3	1.6 (0.6–4.8)	0.349	0.9 (0.3–3.1)	0.879
Unknown	1.7 (0.3–8.8)	0.518	n a	
Margin Status				
Negative	1		1	
Positive	6.2 (2.1–18.0)	**0.001**	1.7 (0.6–5.2)	0.286
Marginal ≤1 mm	0.9 (0.2–3.9)	0.923	1.2 (0.5–2.8)	0.685
Unknown	3.5 (0.5–26.1)	0.216	3.7 (0.5–27.5)	0.204
Tumour size				
<11 mm	1		1	
11–20 mm	1.7 (0.7–4.4)	0.232	2.8 (0.9–8.8)	0.067
>20 mm	2.2 (0.7–6.5)	0.162	4.1 (1.2–13.8)	**0.020**
Unknown	0.8 (0.2–2.9)	0.777	2.2 (0.7–7.4)	0.187
Low Risk DCIS				
None	1		1	
Yes	0.2 (0.03–1.6)	0.132	3.1 (0.9–10.2)	0.061
Histology contra lateral tumour				
No contra lateral tumour	1		1	
DCIS	5.8 (2.0–16.9)	**0.001**	0.9 (0.1–6.5)	0.908
Invasive carcinoma	1.6 (0.5–5.4)	0.427	0.4 (0.1–3.0)	0.390
Timing radiotherapy after lumpectomy				
<36 days	1		1	
36–56 days	0.8 (0.3–2.1)	0.636	1.6 (0.6–3.8)	0.314
>56 days	1.5 (0.6–3.8)	0.343	3.8 (1.6–9.0)	**0.002**

n a: not available. DCIS: ductal carcinoma in situ.

Table 4
Multivariate Cox proportional analyses Hazard Rate (HR) and confidence interval of ipsilateral breast tumour recurrence overall and according to boost versus no boost radiotherapy.

Characteristics	All Patients n = 1248 (%) HR (95% CI)	P value	No-boost group n = 509 HR (95% CI)	P value	Boost group n = 739 HR (95% CI)	P value
Age						
≤51 years	1		1		1	
>50 years	0.4 (0.3–0.8)	**0.004**	0.5 (0.2–1.1)	0.105	**0.3 (0.2–0.7)**	**0.004**
Localisation primary						
Lateral upper quadrant			1		1	
Lateral lower quadrant			0.7 (0.2–3.2)	0.640	2.3 (0.6–8.6)	0.200
Medial upper quadrant			1.4 (0.5–3.8)	0.507	1.9 (0.7–4.8)	0.184
Medial lower quadrant			1.3 (0.3–6.1)	0.748	2.2 (0.5–7.9)	0.226
Central			1.1 (0.2–3.5)	0.891	**3.6 (1.4–9.0)**	**0.006**
Unknown			5.9 (1.0–28.1)	0.037	n a	
Re-excision						
None	1		1		1	
Yes	1.5 (0.8–2.6)	0.189	1.5 (0.6–3.8)	0.385	1.9 (0.8–4.4)	0.145
Margin Status						
Negative	1		1		1	
Positive	**2.8 (1.3–6.0)**	**0.009**	**7.2 (2.1–23.3)**	**0.001**	2.0 (0.6–6.4)	0.228
Marginal ≤1 mm	1.1 (0.5–2.4)	0.725	0.9 (0.2–3.8)	0.861	1.5 (0.6–3.8)	0.376
Unknown	1.9 (0.4–8.8)	0.400	3.5 (0.4–29.4)	0.241	2.1 (0.2–18.8)	0.492
Tumour size						
<11 mm	1		1		1	
11–20 mm	2.0 (1.0–4.1)	0.053	1.4 (0.5–3.8)	0.481	**3.2 (1.0–10.0)**	**0.050**
>20 mm	**2.3 (1.0–5.0)**	**0.044**	1.8 (0.6–5.9)	0.297	**3.6 (1.0–12.3)**	**0.040**
Unknown	1.2 (0.5–2.7)	0.682	0.6 (0.2–2.2)	0.395	1.9 (0.6–6.8)	0.284
Histology contra lateral tumour						
No contra lateral tumour			1		1	
DCIS			**5.5 (1.7–17.8)**	**0.004**	1.2 (0.2–9.4)	0.825
Invasive carcinoma			1.8 (0.5–6.4)	0.352	0.4 (0.05–3.2)	0.394
Timing radiotherapy after lumpectomy						
<36 days	1		1		1	
36–56 days	1.1 (0.5–2.1)	0.827	0.7 (0.2–1.9)	0.420	1.4 (0.6–3.6)	0.458
>56 days	1.9 (1.0–3.8)	0.060	1.0 (0.3–2.9)	0.974	2.5 (0.9–6.9)	0.081

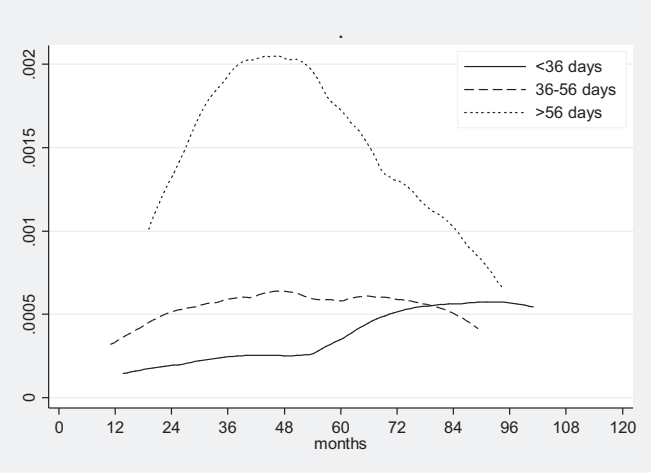

Fig. 3. The Ipsilateral Breast Tumour (IBTR) estimates according to timing of radiotherapy after lumpectomy for those having had a boost with their radiotherapy.

sequential versus SIB, did not show a significant difference for LRFS.

In multivariate Cox regression analysis, as shown Table 4, none of the variables showed significance for either group. For the boost group, age ≤50-years and a central localisation of the primary showed significantly worse LRFS compared to that for older women and those having a lateral upper quadrant localisation. In the no-boost group, a positive margin and a CBT with DCIS showed a significantly worse LRFS compared to that for a negative margin and no CBT, although for both the 95% CI was wide, due to small numbers.

Although highly significant univariate in the boost group, timing of radiotherapy, despite a HR 2.5, was not significant in the multivariate analysis. Fig. 3 shows the IBRT estimates according to timing for the boost group, showing an early recurrence time for those with a timing after 56 days.

3.3. IBTR by prognostic score

The 10-year LRFS for the low-risk DCIS subgroup was not significantly different compared to the rest. According to the subgroups of boost and no-boost, we noted a better LRFS for the low risk patients in the no-boost group compared to the rest, but saw the opposite in the boost group, both not significant univariate and multivariate, Tables 3 and 4

The LRFS for the patients' prognostic score showed a gradual increase in response to every point although this was not significant; see Table 5.

3.4. Disease-specific survival (DSS)

Of all 1248 patients seven patients died due to breast cancer; of those six as a result of IBTR and one patient due to CBT with IC. The overall 10-year DSS was 99.0%; 98.4% for those who had received no boost and 99.6% for those who had received a boost. The 10-year DSS according to the histology of the IBTR was 97.1% for DCIS-recurrence versus 83.7% for IC-recurrence. Patients with a low-risk DCIS had a 100% 10-years DSS compared to 98.9% for no low risk DCIS.

3.5. Contra lateral breast tumour (CBT)

Of all 1248 patients with primary DCIS, 9.1% (113/1248)

Table 5
Hazard ratios and confidence interval of local relapse free survival according to the patient prognostic score modified by Smith et al.

Prognostic Score (n = 1248)	Hazard ratio	95% Conf. Interval
Score 0 (53)	1	
Score 1 (193)	1.0	0.2–4.7
Score 2 (300)	1.3	0.3–5.7
Score 3 (254)	1.4	0.3–6.1
Score 4 (113)	2.0	0.4–9.2
Score 5 (12)	4.6	0.6–33.0
Unknown (323)		

developed a CBT; of those, 7.4% (93/1248) had MBBT, and 1.6% (20/1248) had SBBT. The histology of the MBBTs was 65.6% IC and 34.4% DCIS, and for SBBT 90.0% and 10.0%, respectively.

The 10-year LRFS was 90.9% for SBBT and 89.5% for MBBT showing no significant differences compared to unilateral DCIS, namely 93.3%.

In relation to the histology of the CBT, the 10-year LRFS for those patients with a DCIS was 80.4% (HR 2.7; 95% CI 1.1–6.8), and 94.4% for IC (HR 0.9; 95% CI 0.3–2.6) compared to 93.3% for patients with unilateral DCIS. This effect is predominantly seen in the no-boost group; see Tables 3 and 4

4. Discussion

Our study showed an excellent 10- year 99.0% DSS and a 92.9% LRFS overall. At Age ≤50 years, a positive margin, and tumour size were overall significantly related to worse LRFS. Receiving or not receiving a boost showed no relation to LRFS.

Analysing the impact of age on LRFS, our study demonstrated that the turning point was 50 years. However, we did not have the information on menopausal status to consider whether age or menopausal status was the main determinant.

It has been well demonstrated in randomized trials that WBI for DCIS reduces IBTR in approximately 50% of cases [3–7]. The practice of boosting has been demonstrated to provide a significant reduction in IBRT for invasive carcinoma. In the most recent 20-year follow-up report, the cumulative IBTR incidence was 12% with a boost as against 16.4% without a boost [17]. To date, no similar RT boost trials have been published for DCIS. The practice of using a boost in DCIS and the rationale for that is largely extrapolated from the treatment for IC. A recent study including 4131 patients demonstrated a significant benefit from decreasing long-term IBRT with a boost for DCIS of a similar degree to that experienced in IC [18]. Other studies did not show a benefit of boost in patients with DCIS after BCS and WBI [19,20]. However, in many institutes in the Netherlands a boost is given after (sequential) or simultaneous (SIB) with WBI, even with a negative margin. In our population, 59.2% received a boost. Analysis showed that with negative margins, LRFS were the same for the no boost condition (93.2%) and as for the boost condition (94.0%). Furthermore, the recurrence patterns were similar. Only those patients with a positive margin derived a benefit (HR 0.3; 95% CI 0.1–1.0).

Negative margins after BCS for DCIS have been shown to reduce the risk of IBTR [21]. The optimal margin distance (i.e. the threshold necessary to declare a negative margin) remains a topic of debate [22]. Studies on the growth pattern of DCIS have found that multifocal lesions with intervening normal ductal segments are common. No consensus for DCIS margins has yet been published. The maximum margin of normal breast tissue can be obtained through ablative surgery, and yet after ablative surgery no survival advantage over lumpectomy with minimal margin has been reported. Even our patients with a marginal margin, ≤1 mm showed a comparable IBTR to those with a negative margin. Achieving a negative margin, irrespective of the width, with the first lumpectomy seems to be the best prospect for an excellent IBTR irrespective of a boost. Even a re-excision still leads to an increased risk of IBTR. Even though, a significant benefit (HR 0.3) was demonstrated with a boost in the case of a positive margin, having a positive margin remained a significantly worse factor with respect to local control.

Given the outcome for DCIS, many studies have attempted to identify both favourable and unfavourable subgroups of DCIS patients. To investigate the risk of IBTR, we used a patient's prognostic score, which was proposed by Smith et al. [13]. In our study we found that the likelihood of IBTR increased for every point increase in the prognostic score. Although the number of patients in our study is small compared to the study of Smith, including 14,202 patients, it shows the possible relevance of this scoring system. Looking for a definition of the so-called low-risk patients with DCIS, we could not find a generally accepted definition of a low-risk patient. Based on ongoing trials such as LORIS and LORD and the literature, we created our group of low-risk patients, but found only 7.3% of our population to be genuinely low-risk. This small cohort of low-risk patients did not show any better LRFS compared to the remainder of the cohort.

Also comparing boost and no boost in low-risk patients versus the remainder of the patients did not show any benefit for either group of patients. Following the results of this study and others reported in the literature, a boost with negative margins should be omitted to prevent an overtreatment. The extra boost might influence the cosmetic outcome of the BCT. The results of the long-term cosmetic changes after BCT in the EORTC boost versus no boost trial showed us that a boost worsens the change in breast appearance in the first three years, while fibrosis of the breast is also associated with the WBI [10].

Our overall IBTR rate of 7.1% at 10 years is excellent compared to the rates reported in the literature [7,23]. Approximately half of all IBTRs reported in the literature are invasive, which is comparable with our results. An IC-recurrence is associated with a risk of breast cancer mortality, shown in our results by 83.7% DSS for IC compared to 97.1% for DCIS.

Our study showed a 9.1% incidence of CBT, IC or DCIS, which is comparable to that reported in the literature dealing with IC of breast cancer [7,24]. Overall analysis demonstrated no impact on LRFS and DSS as a result of CBT. Looking at the histology of the CBT, we noted a significantly worse LRFS for those patients with a DCIS as CBT compared to those without CBT, in particularly for those receiving no boost. Although we noted a significantly worse effect on LRFS for those having a DCIS as CBT, we have to bear in mind that the numbers are small five IBTR in patients with DCIS as CBT, to draw any meaningful conclusions.

In our study could not confirm a significant effect of timing of radiotherapy on the IBTR rates, despite the observed highly significant effect in the univariate analysis. This might be due to the small number of events and/or the (relative) low number of patients together with the relative short follow-up. On the other hand our results do not support the necessity to start WBI as soon as possible after surgery.

The present study has some potential limitations, including the small number of events, IBTRs. However, it has several strengths, including the large sample size, high quality clinical data, and the long follow-up times.

Conclusion. DCIS of the breast and treated with BCT results in excellent LRFS and DSS. Primary surgical lumpectomy with negative margins followed by WBI seems to be the treatment of choice in DCIS treated with BCS in terms of IBTR.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[2] Integraal Kanker centrum Nederland (IKNL): www.cijfersoverkanker.nl
[3] Cuzick J, Sestak I, Pinder SE, 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;12:21–9.
[4] Warnberg F, Garmo H, Emdin S, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS trial. J Clin Oncol 2014;32:3613–8.
[5] Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumour recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103:478–88.
[6] Donker M, Litiere S, Weritsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence from the EORTC 10853 randomized phase III trial. J Clin Oncol 2013;31:4054–9.
[7] Garg PK, Jakhetiya A, Pandey R, et al. Adjuvant radiotherapy versus observation following lumpectomy in ductal carcinoma in-situ: a meta-analysis of randomized controlled trials. Breast J 2017. Aug 22 Epub ahead of print.
[8] Shah C, Wobb J, Manyam B, et al. Management of ductal carcinoma in situ of the breast. A review. JAMA Oncol 2016;2:1083–8.
[9] Narod SA, Iqbal J, Giannakeas V, et al. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. JAMA Oncol 2015;1:888–96.
[10] Immink JM, Putter H, Bartelink H, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol 2012;23:2591–8.
[11] Boekel NB, Schaapveld M, Gietema JA, et al. Cardiovascular morbidity and mortality after treatment for ductal carcinoma in situ of the breast. JNCI (J Natl Cancer Inst) 2014;106:1–9.
[12] Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol 2016;34:1190–6.
[13] Smith GL, Smith BD, Haffy BG. Rationalization and regionalization of treatment for ductal carcinoma in situ of the breast. Int J Radiat Oncol Biol Phys 2006;65:1397–403.
[14] Qian GW, Ni XJ, Jiang YZ, et al. Effect of radiotherapy on survival of women with locally excised ductal carcinoma in situ of the breast: a surveillance, epidemiology, and end results population –based analysis. J Dovepress 2015;8:1407–18.
[15] Elshof LE, Tryonidis K, Slaets L, et al. Feasibility of a prospective, randomized, open-label, international multicenter, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ- the LORD study. Eur J Canc 2015;51:1497–510.
[16] Pilewskie M, Olcese C, Patil S, et al. Women with low-risk DCIS eligible for the LORIS trial after complete surgical excision: how low is their risk after standard therapy? Ann Surg Oncol 2016;23:4253–61.
[17] Bartelink H, Maingon P, Poortmans P, et al. Whole breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomized phase 3 trial. Lancet Oncol 2015;16:47–56.
[18] Moran MS, Zhao Y, Ma S, et al. Association of radiotherapy for ductal carcinoma in situ with local control after whole breast radiotherapy. JAMA Oncol 2017;3:1060–7.
[19] Rakovitch E, Narod SA, Nofech-Moses S, et al. Impact of boost radiation in the treatment of ductal carcinoma in situ: a population-based analysis. Int J Radiat Oncol Biol Phys 2013;86:491–7.
[20] Cutuli B, Wiezzane N, Palumbo I, et al. Breast-conserving treatment for ductal carcinoma in situ: impact of boost and tamoxifen on local control. Canc Radiother 2016;(20):292–8.
[21] Wang SY, Chu H, Shamliyan T, et al. Network meta-analysis of margin threshold for women with dutal carcinoma in situ. J Natl Cancer Inst 2012;104:507–16.
[22] Marinovich ML, Azizi L, Macaskill P, et al. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2016;23:3811–21.
[23] Stuart KE, Houssami N, Taylor R, et al. Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis. BMC Canc 2015;15:890.
[24] Jobsen JJ, van der Palen J, Ong F, et al. Bilateral breast cancer, synchronous and metachronous; differences and outcome. Breast Canc Res Treat 2015;153:277–83.