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Original Article

Variation in the Use of Boost Irradiation in Breast-Conserving Therapy in the Netherlands: The Effect of a National Guideline and Cofounding Factors☆

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Abstract

Aims: To determine the variation in radiation therapy boost use in a nationwide study following adjustment of a national guideline in 2011, as well as to address the relationship to patient, tumour and radiation therapy institutional factors.
Materials and methods: All invasive breast cancers and non-invasive breast cancers (ductal carcinoma *in situ*; DCIS) that received external whole-breast radiation between 2011 and 2016 were selected from the Netherlands Cancer Registry. Box plots were used to evaluate variation over time and logistic regression was carried out to address other factors influencing the variation. Funnel plots were constructed, with unadjusted and adjusted data for patient and tumour factors significantly affecting the use of a boost.
Results: For breast cancer patients ($n = 45{,}207$), the proportion receiving a boost and its range decreased over the years from 37.3–92.7% in 2011 to 28.3–65.4% in 2016. This trend was not observed in DCIS patients ($n = 6{,}844$). Young age, large tumours, high grade and the absence of tumour-free resection margins were associated with boost use for both breast cancer and DCIS. For breast cancer, triple-negative tumour subtype and metastatic lymph node involvement were also associated with boost use. Institutional factors did not influence the use of a boost and institutional variation remained substantial after case-mix adjustments.
Conclusion: Following adjustment of a nationwide implemented guideline, variation in radiation therapy boost use decreased in patients with breast cancer but not in patients with DCIS. Several tumour and patient characteristics were associated with boost use. Substantial institutional variation could not be explained by differences in patient, tumour or predefined institutional characteristics.

Key words: Boost; breast cancer; breast-conserving therapy; radiation therapy; whole-breast irradiation

Introduction

Since the introduction of breast-conserving therapy (BCT) in the Netherlands in the early 1980s, radiation therapy typically consisted of whole-breast irradiation (WBI; 50 Gy or equivalent dose) followed by a boost to the

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tumour bed (16 Gy or equivalent dose) in all cases. Breast-conserving surgery (BCS) is carried out in 60% of invasive breast cancer patients and in 67% of patients with a ductal carcinoma *in situ* (DCIS) [1].

The debate about the clinical relevance of the use of a boost has a long history. A boost dose was applied in almost 100% of patients during the 1980s. This endorsed the European Organization for Research and Treatment of Cancer (EORTC) to start the 'Boost/No Boost' trial in 1988, of which the 5-year results were published in 2001 [2]. Thereafter, a boost was gradually given less frequently [3].

In breast cancer, boost use improved local control in all age groups after a median follow-up period of 17.2 years [2]. Patients 40 years and younger had the most benefit in absolute figures: at 10 years of follow-up the local recurrence rate was 23.9% without a boost, compared with 13.5% when a boost was given [4,5]. On the other hand, patients with a boost had a significantly higher risk of severe fibrosis in comparison with patients who did not have a boost (4.4% versus 1.6%) [2,4]. In a second EORTC trial, the presence (or absence) of a dose effect relationship (10 Gy versus 26 Gy) was tested for breast cancer patients with tumour-positive resection margins. No significant differences in local recurrence rates were noted after a median follow-up period of 11.3 years [6].

Various studies have shown an independent effect of various clinicopathological factors on the risk of ipsilateral breast tumour recurrence (IBTR) and hence suggest that a number of these factors can be used to advise on the application of a boost [4,7–9]. For DCIS, convincing evidence about the efficacy of the use of a boost in combination with WBI is lacking. The use of a boost is associated with an increase of fibrotic changes and (hence) a worse cosmetic outcome [10]. In addition, boost contouring and boost planning techniques may vary between institutes in the Netherlands (and abroad), but we did not study this subject [11–20].

In Dutch clinical practice in 2011, large variation in the application of boost was observed for patients with breast cancer, as well as for DCIS, as was shown by nationwide data from the NABON Breast Cancer Audit (NBCA) [1].

The necessity of (re)defining guidelines concerning the use of a boost was acknowledged by the Dutch National Platform for Radiation Therapy for Breast Cancer (LPRM). The LPRM defined evidence-based recommendations when to omit a boost in the treatment of breast cancer. These national guidelines were published in 2011. No such recommendations concerning a boost dose (yes or no) in DCIS could be defined in the absence of sufficient evidence. The LPRM recommended that the benefits of a boost should be weighed against age, co-morbidity and the risk of adverse cosmetic effects and that additional boost should be applied in breast cancer patients when one or more of the following indications was present: age <50 years, an estimated local recurrence risk $\geq 1\%$ per year, a grade 3 breast cancer, the absence of tumour-free resection margins and lymph vascular space invasion [21].

The aim of the present study was to determine the use of a boost in breast cancer as well as the variation in use between the various departments of radiation oncology after the introduction of the new national guidelines. We also aimed to determine the use of a boost in DCIS, as well as its variation between the various departments of radiation oncology. In addition, for breast cancer and DCIS, the association between the use of a boost and patient, tumour and institutional factors was evaluated.

Materials and Methods

Data Source

Patients with primary stage I–III breast cancer or DCIS, based on the seventh edition of the TNM Classification of Malignant Tumours, were selected from the Netherlands Cancer Registry (NCR), which registers data for the NBCA. The NBCA is a nationwide multidisciplinary quality improvement registry in which all hospitals ($n = 92$) and departments of radiation oncology ($n = 21$) in the Netherlands participate. It includes information concerning the patient, tumour, work-up, treatment and outcome. The information has been collected prospectively since 2011, either by the hospital registrars or by data managers of the NCR, which is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). For this study, data from all departments of radiation oncology were obtained through the NCR.

Study Population

Data gathered in all departments of radiation oncology ($n = 21$) regarding all female patients diagnosed as having breast cancer or DCIS and locally treated by BCT between 1 January 2011 and 31 December 2016 were selected. Patients with, as well as those without, primary systemic therapy were included. Patients diagnosed with a synchronous second primary breast cancer or DCIS in the ipsilateral breast or in the contralateral breast and subsequently treated by BCT were included two times.

Statistical Analyses

Analyses for breast cancer and DCIS cases were conducted separately. Analysis was carried out on a tumour level, rather than on a patient level. Boxplots were constructed to show the variation in department-dependent use of a boost over time. Multilevel logistic regression analyses were used to address factors potentially influencing the use of a boost, taking patient clustering within hospitals into account. Factors that were tested were: age (<50, 50–60, 60–70, >70 years), pathological tumour size (<10, 10–20, 20–30, >30 mm), the presence of DCIS adjacent to the invasive part of the tumour in breast cancer patients, histological type (ductal, lobular, mixed, other), tumour grade according to Bloom Richardson (grade 1, 2, 3), triple negativity (no or yes), Her2 receptor status (negative, positive), tumour resection margins (clear margins, tumour not touching ink [R0], close margins, microscopic residual

disease and macroscopic residual disease, R1 and R2, respectively) and tumour involvement of lymph nodes (no, yes or unknown). Lymph vascular space invasion was not taken into account in this study, as this item was not registered systematically. We also investigated whether the type of radiation oncology department (university, independent or hospital related) and mean number of breast cancer patients treated annually (low: <450 patients, medium: 450–650, high: >650) were associated with boost use. Patient, tumour and departmental factors in relation to the use of a boost, were presented as odds ratios for the respective categories of these factors with 95% confidence intervals. Factors that were significantly associated with the use of a boost in univariable analyses ($P < 0.05$) were subsequently analysed in the multivariable analyses. Funnel plots were constructed with unadjusted and adjusted data for patient and tumour factors significantly affecting the use of a boost. All statistical analyses were performed in STATA (version 13.1 2013, Texas).

Results

Study Population

During the study period, 52,051 tumours of 50,116 patients were included and treated by BCS and WBI for stage I–III breast cancer ($n = 45{,}207$) or for DCIS ($n = 6{,}844$). Patient and tumour characteristics are shown in Table 1. Most patients were aged 50 years and older and had pathologically assessed tumour sizes ranging from 0 to 20 mm. For breast cancer and DCIS, most patients had a grade 2 or 3 tumour. More than 90% of the operations for breast cancer and DCIS resulted in tumour-negative resection margins (R0 resection). For breast cancer, 74.3% of the cases had no lymph node involvement.

Variation

In total, 50.6% of the breast cancer patients and 45.7% of the DCIS patients received a boost (Table 1). Variation in the application of a boost was observed between the 21 departments for both breast cancer and DCIS. Over the years 2011–2016, the proportion of patients receiving a boost and the accompanying institutional variation in boost use in breast cancer decreased. The median annual proportion of patients who received a boost decreased from 55.3% in 2011 to 43.5% in 2016 and the range of the institutional proportions also decreased from 37.3–92.7% in 2011 to 28.3–65.4% in 2016 (Figure 1). For DCIS, both overall use (41.9% in 2011, 40.7% in 2016) as well as institutional variation (4.6–100.0% in 2011 to 0.0–80.5% in 2016) hardly varied over time (Figure 1).

Breast Cancer

Factors significantly influencing the use of a boost for breast cancer in univariable analyses are listed in Table 2.

Table 1
Baseline characteristics of all 52,051 invasive breast cancer or ductal carcinoma *in situ* (DCIS) lesions included in this study

		Study population ($n = 52{,}051$)			
		Invasive breast cancer ($n = 45{,}207$)		DCIS ($n = 6{,}844$)	
		No.	%	No.	%
Boost	No	22,337	49.4	3,718	54.3
	Yes	22,870	50.6	3,126	45.7
Age (years)	0–50	9,680	21.4	1,058	15.5
	50–60	12,557	27.8	2,363	34.5
	60–70	15,088	33.4	2,471	36.1
	>70	7,882	17.4	952	13.9
Size (mm)	0–10	14,949	33.1	1,387	20.3
	10–20	21,366	47.3	1,067	15.6
	20–30	6,735	14.9	519	7.6
	>30	1,527	3.4	329	4.8
	Unknown	630	1.4	3,542	51.8
DCIS component	No	23,019	50.9	–	–
	Yes	22,148	49.0	–	–
	Unknown	40	0.1	–	–
Histological type	Ductal	38,268	84.7	–	–
	Lobular	3,852	8.5	–	–
	Mixed	981	2.2	–	–
	Other	2,106	4.7	–	–
Grade	1	12,541	27.7	840	12.3
	2	19,243	42.6	2,595	37.9
	3	10,064	22.3	3,131	45.7
	Unknown	3,359	7.4	278	4.1
Triple negative	No	40,656	89.9	–	–
	Yes	4,551	10.1	–	–
Her2	Negative	39,477	87.3	–	–
	Positive	4,766	10.5	–	–
	Dubious	141	0.3	–	–
	Unknown	823	1.8	–	–
Tumour resection margin	R0	42,475	94.0	6,264	91.9
	R1	2,364	5.2	474	6.9
	R2	160	0.4	36	0.5
	Unknown	208	0.5	70	1.0
Involved lymph nodes	No	33,590	74.3	–	–
	Yes	10,652	23.6	–	–
	Unknown	965	2.1	–	–

After multivariable logistic regression analyses, all patient- and tumour-related factors remained statistically significant, except histological type (Table 2). Patients aged >70 years received a boost significantly less often in comparison with patients aged <50 years. Larger tumours and tumours of a higher malignancy grade were associated with more frequent use of a boost. A DCIS component was also positively associated with the use of a boost. A boost was administered more often in patients with unfavourable molecular subtype tumours (triple-negative and Her2-positive tumours). Microscopic incomplete tumour resection margins were strongly associated with the use of a boost. Finally, involved lymph nodes were also positively related with the use of a boost compared with no lymph

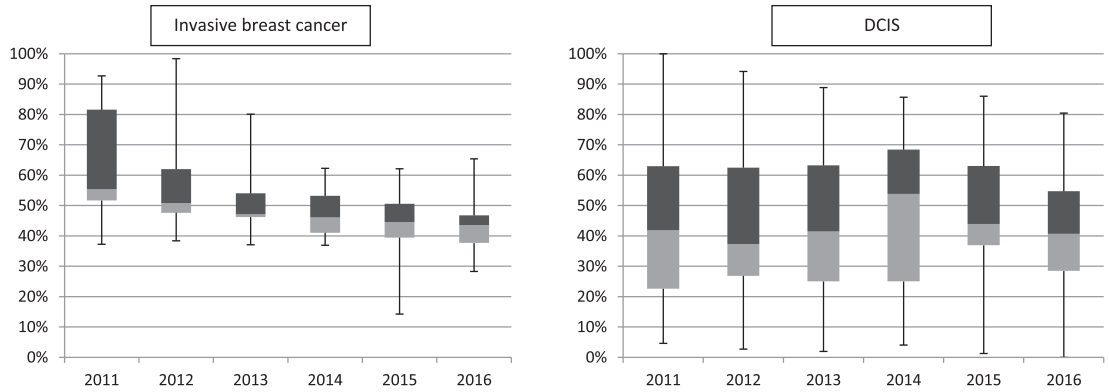

Fig 1. Variation in the use of boost irradiation over the period 2011–2016 after breast-conserving therapy for non-metastatic invasive breast cancer (left) and ductal carcinoma *in situ* (right).

Table 2
Patient- and tumour-related factors determining the use of boost irradiation for non-metastatic invasive breast cancer lesions ($n = 45{,}207$) for the whole period 2011–2016 and for 2011 and 2016 separately

		Boost	%	Total	2011–2016 ($n = 45{,}207$)				2011 ($n = 7{,}048$)		2016 ($n = 7{,}697$)	
					Univariable		Multivariable		Multivariable		Multivariable	
					OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Patient/tumour characteristics												
Age (years)	0–50	8,232	85.0	9,680	Reference		Reference		Reference		Reference	
	50–60	6,439	51.3	12,557	0.18	0.16–0.19	**0.17**	0.16–0.18	**0.30**	0.25–0.36	**0.11**	0.10–0.14
	60–70	5,912	39.2	15,088	0.10	0.10–0.11	**0.10**	0.09–0.11	**0.17**	0.14–0.21	**0.07**	0.06–0.08
	>70	2,287	29.0	7,882	0.07	0.06–0.07	**0.05**	0.05–0.06	**0.06**	0.05–0.08	**0.05**	0.04–0.06
Size (mm)	0–10	6,553	43.8	14,949	Reference		Reference		Reference		Reference	
	10–20	10,777	50.4	21,366	1.28	1.23–1.34	**1.16**	1.10–1.22	0.97	0.84–1.11	**1.37**	1.19–1.58
	20–30	4,185	62.1	6,735	2.04	1.92–2.17	**1.33**	1.24–1.44	1.05	0.86–1.28	**1.56**	1.28–1.90
	>30	1,018	66.7	1,527	2.53	2.26–2.84	**1.62**	1.41–1.87	0.99	0.67–1.45	**2.66**	1.87–3.78
	Unknown	337	53.5	630	1.53	1.31–1.80	0.95	0.77–1.16	**0.55**	0.33–0.92	1.68	0.90–3.11
DCIS component	No	10,581	46.0	23,019	Reference		Reference		Reference		Reference	
	Yes	12,273	55.4	22,148	1.47	1.41–1.52	**1.66**	1.58–1.74	**1.45**	1.28–1.64	**1.95**	1.72–2.22
	Unknown	16	40.0	40	0.92	0.49–1.75	0.48	0.22–1.07	**0.18**	0.05–0.59		
Histological type	Ductal	19,917	52.0	38,268	Reference		Reference		Reference		Reference	
	Lobular	1,539	40.0	3,852	0.61	0.57–0.65	0.92	0.84–1.00	1.10	0.88–1.38	0.93	0.74–1.15
	Mixed	462	47.1	981	0.85	0.75–0.97	0.99	0.85–1.16	1.05	0.71–1.54	0.88	0.59–1.32
	Other	952	45.2	2,106	0.76	0.69–0.83	1.06	0.95–1.18	1.08	0.81–1.44	0.94	0.71–1.26
Grade	1	4,387	35.0	12,541	Reference		Reference		Reference		Reference	
	2	8,163	42.4	19,243	1.36	1.30–1.43	**1.25**	1.18–1.32	1.13	0.98–1.31	**1.28**	1.10–1.49
	3	8,200	81.5	10,064	8.54	8.01–9.10	**8.21**	7.59–8.88	**3.68**	3.00–4.50	**13.42**	10.96–16.44
	Unknown	2,120	63.1	3,359	3.27	3.02–3.55	**2.43**	2.20–2.68	**1.73**	1.33–2.25	**2.26**	1.63–3.15

(*continued on next page*)

Table 2 (*continued*)

		Boost	%	Total	2011–2016 (n = 45,207)				2011 (n = 7,048)		2016 (n = 7,697)	
					Univariable		Multivariable		Multivariable		Multivariable	
					OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Triple negative	No	19,480	47.9	40,656	Reference		Reference		Reference		Reference	
	Yes	3,390	74.5	4,551	3.28	3.05–3.51	**1.41**	1.28–1.54	**1.36**	1.07–1.73	**1.81**	1.43–2.27
Her2	Negative	19,350	49.0	39,477	Reference		Reference		Reference		Reference	
	Positive	3,164	66.4	4,766	2.08	1.95–2.22	**1.14**	1.05–1.24	**1.65**	1.33–2.04	0.96	0.78–1.18
	Dubious	61	43.3	141	0.88	0.63–1.24	1.09	0.72–1.65	1.77	0.60–5.23	0.99	0.28–3.45
	Unknown	295	35.8	823	0.55	0.47–0.64	**0.77**	0.64–0.91	0.91	0.58–1.43	**0.52**	0.31–0.87
Tumour resection margin	R0	20,447	48.1	42,475	Reference		Reference		Reference		Reference	
	R1	2,159	91.3	2,364	11.86	10.25–13.71	**21.54**	18.45–25.15	**12.17**	8.12–18.25	**51.74**	34–52–77.55
	R2	129	80.6	160	5.09	3.43–7.56	**8.98**	5.80–13.90	**4.52**	1.65–12.34	**13.28**	4.88–36.12
	Unknown	135	64.9	208	1.99	1.49–2.65	**1.63**	1.15–2.29	1.75	0.68–4.51	1.39	0.44–4.32
Involved lymph nodes	No	15,905	47.4	33,590	Reference		Reference		Reference		Reference	
	Yes	6,508	61.1	10,652	1.75	1.67–1.83	**1.42**	1.34–1.50	**1.28**	1.11–1.48	**1.40**	1.21–1.62
	Unknown	457	47.4	965	1.04	0.91–1.19	**1.25**	1.07–1.46	**2.02**	1.15–3.55	**1.55**	1.13–2.14
Department characteristics												
Department of radiation oncology type	University	11,565	50.9	22,705	Reference							
	Independent	7,641	51.3	14,884	1.12	0.80–1.56						
	Hospital related	3,664	48.1	7,618	0.86	0.62–1.20						
Department of radiation oncology volume (patients treated yearly)	Low	8,237	51.3	16,061	Reference							
	Medium	7,546	50.3	15,001	1.02	0.73–1.42						
	High	7,087	50.1	14,145	1.01	0.69–1.48						

DCIS, ductal carcinoma *in situ*; OR, odds ratio; 95%CI, 95% confidence interval.
P values < 0.05 are in bold.

involvement. Departmental patient volume and hospital type did not affect the proportion of patients who received a boost.

Age, DCIS component, grade, triple negativity, tumour resection margin and lymph node involvement were positively associated with the use of a boost in 2011 as well as in 2016, but the association was more pronounced in 2016. In 2016, tumour size was significantly influencing the use of boost, whereas this was not the case in 2011. For Her2-positive tumours, a significant positive association in the use of a boost was found in 2011 only.

Figure 2 shows the variation between the departments of radiation oncology for the use of a boost for breast cancer. Following case-mix adjustments for patient and tumour factors (age, tumour size, DCIS component, grade, triple negativity, Her2-positive tumour, tumour resection margin, pathological lymph node involvement) institutional variation remained significant (40.0–68.2%).

Ductal Carcinoma in Situ

Factors significantly influencing the use of a boost for DCIS in univariable analyses are displayed in Table 3. In the multivariable logistic regression analyses, most significant univariable factors remained statistically significant (Table 3). Patients aged >70 years had a significantly lower chance of receiving a boost in comparison with patients aged <50 years. The probability of receiving a boost decreased with increasing age. The probability of receiving a boost increased as tumour size increased. Patients with a pathologically assessed size of DCIS >1 cm were more likely to receive a boost compared with patients with a lesion <1 cm. Grade 3 lesions were strongly associated with an increased use of a boost compared with grade 1 lesions. Microscopic positive tumour resection margins were strongly associated with the use of a boost compared with tumour-free resection margins. All lesions and patient-

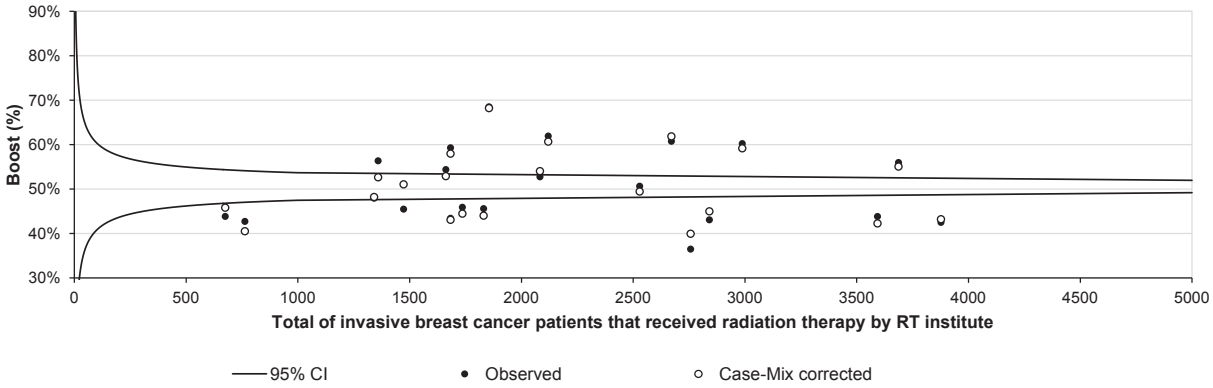

Fig 2. Variation in the use of boost irradiation after breast-conserving therapy for invasive breast cancer in the Netherlands over the years 2011–2016, with (white dots) and without (black dots) case-mix adjustment (for age, tumour size, ductal carcinoma *in situ* component, grade, triple negativity, Her2-positive tumour, tumour resection margin, pathological lymph node involvement) (n = 45,207).

related factors were positively related with the use of a boost from 2011 to 2016, but for almost all factors these associations were higher in 2016. As for breast cancer, case-mix adjustments for patient and lesion factors (age, tumour size, grade, tumour resection margin) decreased the variation between departments in the use of a boost for DCIS only marginally (data not shown).

Discussion

The addition of a boost to WBI has an established risk-reducing effect on local recurrence. Randomised trials have shown a relative risk reduction of the additional boosting of about 35% for all breast cancer patients and a high absolute benefit in young breast cancer patients (<41 years) [4,5]. At the same time, the addition of a boost compromises the cosmetic outcome of treatment through a higher risk of developing fibrosis of the irradiated breast tissue.

Since the revisions of the Dutch guidelines in 2011, it is recommended to use a boost for breast cancer patients with an estimated local recurrence risk ≥1% per year and commonly advised in patients aged <50 years [21]. Following the publication of the guideline, a 20% decrease was observed of the proportion of breast cancer patients who received additional boosting over a 5-year time period. The variation in boost use between institutions decreased as well. For DCIS patients, these trends were not observed. We think that this finding can be explained by the lack of phase III trials in DCIS cases.

A reduction in variation between institutions has proven to be an important target for the improvement of medical practice [22]; variation that is not associated with differences in tumour characteristics, patient factors or patients' preferences may lead to underuse of adequate care and to suboptimal outcomes [22]. This highlights the relevance of studying clinical practice variation leading to a growing interest in addressing variation in medical practice in terms of guideline adherence [22,23].

Breast Cancer

In breast cancer patients, the observed variation between the radiation oncology departments in the use of a boost decreased during the study period, but persisted to some extent. It is unlikely that unfamiliarity with, or negligence of, the 2011 guidelines played a major role. The interplay between surgical management and radiation therapy in patients with focally positive tumour resection margins may have had an effect on the remaining institutional variation. In Dutch clinical practice, a radiation therapy boost after a microscopically (R1) positive tumour resection margin is common [24], an approach that may differ compared with other countries, where a re-excision is preferred. Then again, a recent nationwide study showed that about 50% of all BCS patients with a focally positive tumour resection did undergo a second operative procedure [24]. This may have had an impact on the observed variation in radiation therapy boosting. Nevertheless, surgical re-excision rates in the Netherlands have decreased over the same period as the proportion of patients who received boost radiation therapy decreased [1].

All in all, opinions as to what is considered a clinically meaningful reduction in risk of local recurrences apparently differ between institutions (or radiation oncologists). Recent data about the overall 5-year risk of local recurrence following BCS in the Netherlands were as low as 2.5%, translating into an annual IBTR risk of 0.5% [25]. The observation that systemic treatment as well as molecular subtype importantly influenced the risk of recurrence and mitigated the effect of age [26], possibly contributes to the disagreement whether a meaningful reduction of recurrence risk can be achieved by an additional boost. Uniform risk prediction tools for IBTR could possibly contribute to less variation in the use of boost between the departments, for example 'IBTR! 2.0' [27]. Moreover, decision aid tools for patients illustrating the possible consequences of certain choices could be useful in shared decision making and reduce unwanted variations for preference-sensitive health care options, such as boost radiation therapy [28]. We agree

Table 3
Patient- and tumour-related factors determining the use of boost irradiation for ductal carcinoma *in situ* (DCIS; $n = 6{,}844$) for the whole period 2011–2016 and for 2011 and 2016 separately

		Boost	%	Total	2011–2016 ($n = 6{,}844$)				2011 ($n = 1{,}004$)		2016 ($n = 1{,}153$)	
					Univariable		Multivariable		Multivariable		Multivariable	
					OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Patient/tumour characteristics												
Age (years)	0–50	595	56.2	1,058	Reference		Reference		Reference		Reference	
	50–60	1,190	50.4	2363	0.76	0.64–0.90	**0.63**	0.52–0.75	**0.63**	0.48–0.82	**0.77**	0.49–1.20
	60–70	1048	42.4	2,471	0.51	0.43–0.60	**0.39**	0.32–0.46	**0.45**	0.35–0.59	**0.34**	0.22–0.54
	>70	293	30.8	952	0.26	0.21–0.32	**0.16**	0.13–0.21	**0.18**	0.13–0.26	**0.19**	0.11–0.33
Size (mm)	0–10	520	37.5	1,387	Reference		Reference		Reference		Reference	
	10–20	504	47.2	1,067	1.74	1.45–2.09	**1.63**	1.34–1.99			**1.80**	1.23–2.64
	20–30	290	55.9	519	2.71	2.15–3.42	**2.20**	1.70–2.85			**2.23**	1.40–3.57
	>30	192	58.4	329	3.11	2.36–4.10	**2.45**	1.81–3.33			**2.41**	1.38–4.20
	Unknown	1,620	45.7	3,542	1.48	1.28–1.71	**1.34**	1.15–1.57			1.08	0.65–1.81
Grade	1	279	33.2	840	Reference		Reference		Reference		Reference	
	2	1,101	42.4	2,595	1.50	1.25–1.80	**1.72**	1.40–2.10	1.32	0.80–2.18	**3.01**	1.66–5.44
	3	1,666	53.2	3,131	2.81	2.35–3.37	**3.46**	2.83–4.23	**2.50**	1.53–4.10	**7.25**	4.00–13.15
	Unknown	80	28.8	278	0.79	0.57–1.10	1.07	0.75–1.53	1.03	0.43–2.45	1.29	0.36–4.57
Tumour resection margin	R0	2,624	41.9	6,264	Reference		Reference		Reference		Reference	
	R1	431	90.9	474	19.18	13.59–27.07	**26.47**	18.42–38.04	**26.22**	9.79–70.18	**37.79**	10.84–83.40
	R2	31	86.1	36	8.72	3.28–23.17	**11.90**	4.25–33.36	**11.30**	1.07–118.99	Omitted	
	Unknown	40	57.1	70	1.98	1.15–3.41	**2.24**	1.28–3.93	1.61	0.27–9.78	**17.31**	2.86–104.85
Department characteristics												
Department of radiation oncology type	University	1,485	42.2	3,515	Reference		Reference					
	Independent	1,109	51.4	2,157	1.58	0.50–5.05						
	Hospital related	532	45.4	1,172	1.33	0.42–4.27						
Department of radiation oncology volume (patients treated yearly)	Low	1,052	43.5%	2,421	Reference		Reference					
	Medium	873	37.8%	2,310	0.69	0.23–2.08						
	High	1,201	56.8%	2,113	1.61	0.46–5.68						

OR, odds ratio; 95%CI, 95% confidence interval.
P values < 0.05 are in bold.

with Bartelink *et al.* [4] that the expected gain in local control (IBTR) and the negative cosmetic effects of the boost should be discussed with patients on an individual basis. Surgery-associated considerations could have contributed to the observed variation as well, e.g. the individually based omission of the boost if the target volume could not be reconstructed reliably following extensive surgery or in the presence of a large seroma of haematoma [29].

The overall rate of patients receiving a boost in addition to WBI following BCS for breast cancer declined from almost 100% in the 1980s to 55% in 2011 and further decreased to 43% in 2016. Known risk factors for local recurrence such as young age, higher malignancy grade, metastatic lymph node involvement and a tumour-positive resection margin [30–33] were all associated with boost use in the present study. As the institutional variation to apply a boost decreased over time, the association between boost application and the various risk factors became stronger, implying improved guideline-directed deployment of boost at the end of the study period. Following case-mix correction for the aforementioned clinicopathological factors, considerable variation remained in breast cancer patients that was not explained by institutional characteristics such as patient volume and academic orientation of a particular institute.

Notwithstanding the decreased proportion of patients who receive a boost as part of BCT, the use of a boost at the end of the study period is still high (43%). This figure is to be placed in its historical national context as trial participation in the aforementioned 'boost versus no boost trials' was very high in the Netherlands (about 100%) and the

conclusions of the respective phase III trials were early adopted by many radiation therapy departments in our country. National guidelines recommended boost radiation therapy as an alternative to surgical re-excision for patients with focally positive margins as early as 2002 and the relatively common use of boost is to be seen in the perspective of a very low proportion of all patients undergoing BCS who require a second operative procedure (about 7%, based on data from the NBCA [1]).

Ductal Carcinoma in Situ

In DCIS patients, the substantial interinstitutional variation remained throughout the study period. No association with the type of radiation oncology department or patient volume and no decrease in the proportion of patients treated by additional boost was observed. The 2011 guideline adjustment that included no particular recommendations regarding DCIS and the absence of phase III trials concerning the efficacy of a boost dose for DCIS are important explanations for the persisting variation. Historically, systemic treatment is not advocated or used in the Netherlands and surgical guidelines are strict in terms of advising secondary surgery for (even focally) positive tumour resection margins. Despite the lack of evidence for using a boost for DCIS, 40% of all patients who underwent BCS for DCIS received an additional boost following a radical resection and patients with larger DCIS areas and of higher grade were more likely to have an additional boost. Invasive cancer treatment guidelines are to a substantial extent extrapolated to the treatment of DCIS. Recent international guidelines being more liberal regarding an acceptable tumour resection margin (where 2 mm was considered to be sufficient) will probably affect future boost use and so will the tendency to treat low and intermediate grade DCIS by a wait and see policy [34,35]. Previous retrospective cohort studies showed that a boost confers a statistically significant benefit in decreasing IBTR for DCIS patients and is similar for patients with breast cancer [36,37]. However, as these studies included patients diagnosed with DCIS up to more than 20 years ago, current practices in surgery and systemic treatments may differ. Recently completed clinical trials that further explored the benefit of a boost for DCIS will provide results in the coming years. We expect that this higher level of evidence concerning the effect of a boost for DCIS will reduce the variation between radiation oncology departments.

The population-based character of the present study is unique and provides insight in the overall use of a boost in daily practice in all 21 departments of radiation oncology in the Netherlands after the introduction of the guideline. However, we have to mention some drawbacks of the study. We were not able to avoid the risk of confounding by severity. Due to incomplete registration of tumour sizes for DCIS in certain years, we had to deal with missing tumour sizes, especially in 2011. The absence of detailed information regarding surgical procedures in relation to resection margins and regarding systemic treatment precluded analysis of the interplay between the radiation therapy techniques and the other treatments. Further research should identify doctors' attitudes towards and patients' preferences regarding the use of a boost and whether these factors explain the variation.

Conclusions

In the Netherlands, substantial variation between departments of radiation oncology was observed of the use of a boost to the primary tumour bed in the framework of BCT in patients with breast cancer and DCIS. The median annual proportion of patients who received a boost and the institutional variation in the use of a boost decreased for breast cancer after the introduction of a new national guideline in 2011. For DCIS, overall use as well as institutional variation persisted over time. The variation could not completely be explained by patient-, tumour- or department-related characteristics. Personal preferences in the various radiation institutions were probably associated with the observed (unchanged) variation in the use of a boost in DCIS patients.

Ethics Approval and Consent to Participate

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require the approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

Availability of Data and Materials

The data that support the findings of this study are available from the Netherlands Comprehensive Cancer Organization, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Netherlands Comprehensive Cancer Organization.

Conflict of interest

The authors declare no conflict of interest.

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