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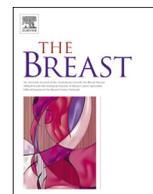
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## Original article

## Factors influencing time between surgery and radiotherapy: A population based study of breast cancer patients



S. Katik<sup>a</sup>, M. Gort<sup>b</sup>, J.J. Jobsen<sup>c</sup>, J.H. Maduro<sup>d</sup>, H. Struikmans<sup>e,f</sup>, S. Siesling<sup>a,b,\*</sup>

<sup>a</sup> Dept. of Health Technology and Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

<sup>b</sup> Dept. of Registration and Research, Comprehensive Cancer Center the Netherlands, Utrecht, The Netherlands

<sup>c</sup> Dept. of Radiotherapy, Medical Spectrum Twente, Enschede, The Netherlands

<sup>d</sup> Dept. of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

<sup>e</sup> Dept. of Radiotherapy, Medical Center Haaglanden, The Hague, The Netherlands

<sup>f</sup> Dept. of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands

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## ABSTRACT

This study describes variation in the time interval between surgery and radiotherapy in breast cancer (BC) patients and assesses factors at patient, hospital and radiotherapy centre (RTC) level influencing this variation. To do so, the factors were investigated in BC patients using multilevel logistic regression. The study sample consisted of 15,961 patients from the Netherlands Cancer Registry at 79 hospitals and 19 (RTCs) with breast-conserving surgery or mastectomy directly followed by radiotherapy. The percentage of patients starting radiotherapy  $\leq 42$  days varied from 14% to 94%. Early year of incidence, higher age, higher stage, mastectomy, higher ASA category and no availability of radiotherapy facilities were significantly associated with a longer time interval between radiotherapy and surgery. More patients received radiotherapy  $\leq 42$  days in hospitals with on-site radiotherapy facilities (OR 1.36,  $p = 0.024$ ). Among the remainder, significant variation was found at the RTC level (11.1%,  $\sigma^2 = 0.254$ , SE 0.054), and at the hospital level (6.4%  $\sigma^2 = 0.443$ , SE 0.163) (ICC 0.064). The significant delay and unexplained variance remaining at the RCT and hospital level suggests delays caused by the patient referral pathway from hospital to RCT, and indicates potential for improvement at both levels.

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## Introduction

Breast cancer (BC), on which surgery is performed in all 91 hospitals in the Netherlands, is the most common type of cancer among women in the country, with more than 14,500 new cases diagnosed in 2014. The first national evidence based breast cancer treatment guideline, developed in 2002 and revised and expanded thereafter, states that radiotherapy is considered an integral part of breast-conserving treatment. After mastectomy, radiotherapy is administered in high-risk cases and is also considered in cases with an intermediate risk of loco regional recurrent disease [1]. In both

settings, the aim of adjuvant radiotherapy is to reduce the risk of local recurrent disease as well as the risk of distant metastases.

In the past 20 years, due to the rising incidence of cancer and indications for radiotherapy treatment [2–4], demand for it has increased. While in some countries the capacity of radiotherapy facilities has not increased, resulting in increasingly long delay [5,6], in the Netherlands the existing lack of capacity in 2000 was addressed and resolved by 2009–2011 [7]. However, the impression in the Netherlands still remains that interval times between surgery and start of radiotherapy are long.

In 2011, the National Breast Cancer Organization the Netherlands (NABON) defined a multidisciplinary set of BC quality indicators. Most of these describe the care process in terms of treatment given according to the guideline and the timeliness of treatment. One of the process indicators is the indicator for adjuvant radiotherapy. This concerns the time interval between the last therapeutic surgical procedure and the start of postoperative radiotherapy, and is defined as the percentage of patients starting radiotherapy  $\leq 42$  days after their surgery [8].

\* Corresponding author. Comprehensive Cancer Center The Netherlands (IKNL), PO Box 19079, 3501 DB Utrecht, The Netherlands. Tel.: +31 88 2345500; fax: +31 88 2345599.

E-mail addresses: [s.katik@iknl.nl](mailto:s.katik@iknl.nl) (S. Katik), [m.gort@iknl.nl](mailto:m.gort@iknl.nl) (M. Gort), [j.jobsen@mst.nl](mailto:j.jobsen@mst.nl) (J.J. Jobsen), [j.h.maduro@umcg.nl](mailto:j.h.maduro@umcg.nl) (J.H. Maduro), [h.struikmans@mchaaglanden.nl](mailto:h.struikmans@mchaaglanden.nl), [hstruikmans@lumc.nl](mailto:hstruikmans@lumc.nl) (H. Struikmans), [s.siesling@iknl.nl](mailto:s.siesling@iknl.nl) (S. Siesling).

In the Netherlands, the variation of the interval time between hospitals as well as factors influencing this time interval has not yet been studied. Insight into these factors could provide directions for improvement. This study therefore aims to describe variation in this time interval and to assess the factors influencing this interval at patient, hospital and radiotherapy centre (RTC) level.

## Patients and methods

### Study population

This study was performed in 79 hospitals (8 academic, 49 general and 22 top clinical hospitals) and 19 RTCs in the Netherlands in the period 2009–2011. The hospitals cover the diagnoses and treatment of about 85% of all BC patients. BC patients were selected from the nationwide population-based Netherlands Cancer Registry (NCR). All data has been obtained from patient files in the hospitals by trained registration assistants and coded according to a national manual. Patient, tumour and treatment characteristics are registered. Topography and morphology are coded according to the (ICD-0-3) and staging according to the TNM classification 7th Edition [9,10]. Since 2011, in addition to the NCR data, more detailed data has been gathered for the NABON Breast Cancer Audit.

Patient selection for this study was according to the NABON indicator definition. From the NCR, all female patients diagnosed with invasive or non-invasive (DCIS) BC without distant metastases who underwent either breast conserving surgery (BCS) or mastectomy with postoperative radiotherapy during the period 2009–2011 were included irrespective of their neo-adjuvant therapy or adjuvant hormone and/or chemotherapy after radiation. Since the Dutch guidelines does not recommend a specific sequence of radiotherapy and chemotherapy, and as the NABON guideline specifies, we excluded patients who received adjuvant chemotherapy before radiotherapy ( $n = 16,269$ ). Patients treated with intra-operative radiotherapy ( $n = 139$ ) and patients for whom the RTC was unknown ( $n = 169$ ) were excluded, resulting in a total of 15,961 BC patients for study.

### Definition of timing of postoperative radiotherapy

Timing of postoperative radiotherapy was according to NABON indicator, namely time from last therapeutic surgery until start of radiotherapy. For patients with axillary lymph node dissection, the date of the axillary dissection was defined as last surgery. The time interval was categorized into two categories:  $\leq 42$  days and  $> 42$  days.

### Measures

The influence of factors on the interval between surgery and start of radiotherapy was determined at three levels: patient, hospital and RTC. At patient level, the variables considered were age, tumour stage and type of surgery. For 2011, palpability, multifocality, type of radiotherapy and ASA score were also available. The American Society of Anesthesiologists (ASA) physical status classification system was used to assess the fitness of patients before surgery. ASA category 1 includes healthy patients (32%), ASA category 2 includes patients with severe diseases (45%), ASA category 3 includes patients with serious illness (ASA-score 3 and 4) (6%).

Variables at hospital level were hospital volume, type of hospital and availability of an on-site radiotherapy facilities. The volume of a hospital was defined as the number of BC surgeries in 2011. Hospitals were divided into  $< 100$  BC surgeries ( $n = 21$ ), 100–200 surgeries ( $n = 39$ ) and more than 200 surgeries ( $n = 19$ ) on average per year. The type of hospital, defined by the hospital where the last therapeutic surgical intervention was conducted, was divided into

three categories: academic hospital ( $n = 8$ ), general hospital ( $n = 49$ ) and top clinical hospital ( $n = 22$ ). Academic hospitals are directly related to an university, involved in education of medical students and focussed on research. Both academic and top clinical hospitals provide medical training to surgical residents. In addition, hospitals were grouped into hospitals with on-site radiotherapy facilities (maximum distance of 1 km of the hospital) and hospitals without radiotherapy facilities. RTCs were classified as independent RTC ( $n = 6$ ), department of a top clinical hospital ( $n = 6$ ) and department of an academic hospital ( $n = 7$ ).

### Data analysis

Differences between the hospitals are represented as funnel plots with two-sigma limits as defined by formula by Spiegelhalter [11]. To test between-group differences for  $\leq 42$  days and  $> 42$  days,  $\chi^2$  tests were used. Multilevel logistic approach was used to evaluate the influence of factors associated with time from surgery to start of radiotherapy. This was applied because multilevel analysis takes into account the hierarchical structure of the data and provides more accurate estimates than traditional regression analysis [12]. The BC patients were nested into hospitals and RTCs. The dependent variable was dichotomized according to the 42 days norm. First, the dataset of patients diagnosed in 2009–2011 was analysed ( $n = 15,961$ ). Next, for a subgroup that included all patients diagnosed in 2011, an additional analysis was performed including the available variables ASA category, multifocality, type of radiotherapy and palpability ( $n = 6495$ ).

In the first stage of the analysis, a null model without any variables was estimated. This model estimates which part of total variance in the dependent variable, timing of radiotherapy, can be assigned to different levels. Next, univariate analysis with a threshold for inclusion of a P-value = 0.10 was performed. Multilevel variable logistic regression analysis with factors significantly related to a time interval of 42 days was performed. Patients, hospital and RTC characteristics that were significant in the univariate analysis were added stepwise into the model. The effects of different variables upon the likelihood of receiving radiotherapy  $\leq 42$  days were expressed in odds ratios (OR) with 95% confidence intervals (CI) and were obtained from the  $\beta$  coefficient and standard error of the model ( $OR = \exp \beta$ ). The size of the variance of a level in combination with standard error (SE) was used as a rough test to judge the significance of the variance. The intra class correlation coefficient (ICC) estimated dependency of observations within a certain level [13].

Since in logistic multilevel analysis the lowest level variance is fixed to the variance of a logistic distribution with a variance of  $\pi^2/3$ , the unexplained variance of the radiotherapy and hospital level can only be interpreted as a proportion of the total unexplained variance [14].

For the multivariable analysis, P-values were considered significant at 0.05. Stata version 12.0 was used for all analyses.

## Results

### Study population

Table 1A presents the patient characteristics, and Table 1B shows the hospital and RTC characteristics together with the percentage of patients with radiotherapy  $\leq 42$  days and  $> 42$  days after surgery. Of the total number of BC patients 68% received radiotherapy  $\leq 42$  days. This improved over time, from 61%  $\leq 42$  days in 2009, to 70% patients in 2011. The median number of days between last surgery and start of radiotherapy was 38 days (interquartile range 32–46 days). Furthermore, 90% received radiotherapy  $\leq 56$

**Table 1A**Patient characteristics and percentage of patients having radiotherapy  $\leq 42$  days after surgery, for the period 2009–2011 and 2011.

Characteristics	2009–2011		P-value	2011		P-value
	$\leq 42$ days, n = 10,790 (%)	$> 42$ days, n = 5171 (%)		$\leq 42$ days n = 4548 (%)	$> 42$ days n = 1947 (%)	
<b>Incidence year</b>						
2011	4548 (42.2)	1947 (37.7)	<0.001			
2010	3465 (32.1)	1453 (28.1)				
2009	2777 (25.7)	1771 (34.2)				
<b>Age</b>						
<50	2054 (19.0)	1145 (22.1)	<0.001	836 (18.4)	409 (21.0)	<0.001
50–59	3338 (30.9)	1447 (28.0)		1358 (29.9)	500 (25.7)	
60–69	3214 (29.8)	1428 (27.6)		1396 (30.7)	542 (27.8)	
70–79	1916 (17.8)	961 (18.6)		825 (18.1)	400 (20.6)	
>80	268 (2.5)	190 (3.7)		133 (2.9)	96 (4.9)	
<b>Stage (pTNM)</b>						
DCIS	1436 (13.3)	581 (11.2)	<0.001	572 (12.6)	217 (11.2)	<0.001
I	6269 (58.1)	2275 (44.1)		2598 (57.0)	834 (42.8)	
II	2372 (22.0)	1569 (30.3)		1055 (23.2)	567 (29.1)	
III	693 (6.4)	731 (14.1)		317 (7.0)	324 (16.6)	
Unknown	20 (0.2)	15 (0.3)		6 (0.1)	5 (0.3)	
<b>Multifocal</b>						
No			<0.001	4164 (91.6)	1677 (86.1)	<0.001
Yes				384 (8.4)	270 (13.9)	
<b>ASA category</b>						
1			<0.001	1559 (34.3)	540 (27.7)	<0.001
2				2091 (46.0)	844 (43.4)	
3				227 (5.0)	142 (7.3)	
Unknown				671 (14.7)	421 (21.6)	
<b>Palpability</b>						
No			<0.001	2035 (44.7)	734 (37.7)	<0.001
Yes				2416 (53.2)	1163 (59.7)	
Unknown				97 (2.1)	50 (2.6)	
<b>Type of surgery</b>						
Breast conserving surgery	9774 (90.6)	4152 (80.3)	<0.001	4094 (90.0)	1517 (77.9)	<0.001
Mastectomy	1016 (9.4)	1019 (19.7)		454 (10.0)	430 (22.1)	
<b>Type of radiotherapy</b>						
Breast/chest wall with boost			<0.001	2411 (53.0)	939 (48.2)	<0.001
Breast/chest wall without boost				1525 (33.5)	622 (31.9)	
Breast/chest wall + with boost regional				205 (4.5)	107 (5.5)	
Breast/chest wall + without boost regional				312 (6.9)	223 (11.5)	
Other				6 (0.1)	6 (0.3)	
Unknown				89 (2.0)	50 (2.6)	

days and 99%  $\leq 84$  days. The tertiles showed a significant difference for incidence year, age, stage, multifocality, ASA category, palpability, type of surgery, type of radiotherapy, Hospital of radiotherapy facilities and type of radiotherapy centre.

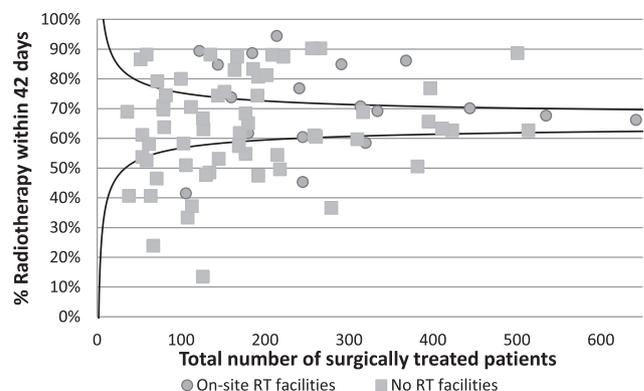
### Patients

A large percentage of the patients (77%) had stage I or stage II BC. The majority underwent breast-conserving surgery (87%). A smaller percentage of patients had radiotherapy after surgery  $\leq 42$  days in case of early year of incidence, higher age, higher stage, a multifocal tumour, a palpable tumour, a higher ASA category, mastectomy and radiotherapy on the breast and chest wall without boost (Table 1A). Of the patients, 47% received adjuvant radiotherapy only, 46% received a combination of adjuvant radiotherapy, hormone therapy and/or chemotherapy, 3% received neo-adjuvant hormone and/or chemotherapy and adjuvant radiotherapy, and 4% received neo-adjuvant hormone and/or chemotherapy and adjuvant radiotherapy, hormone therapy and/or chemotherapy after radiotherapy.

### Hospitals

Of the patients, 49% were operated in general hospitals, 42% in top clinical hospitals, and 9% in academic hospitals. About a quarter of the hospitals (27%) performed less than 100 surgeries on average per year, and 73% performed more than 100. The majority (77%) of

the hospitals had no on-site radiotherapy facilities (Table 1B). The percentage of patients with radiotherapy starting  $\leq 42$  days after surgery varied between hospitals (n = 79) from 14% to 94%. The variation in the time interval across hospitals over the period 2009–2011 is over-dispersed, on the basis of the two-sigma criterion, 22 hospitals were low-outlier and 25 hospitals were high-outlier (Fig. 1). Patients who underwent their treatment in hospitals with on-site radiotherapy facilities more frequently started radiotherapy  $\leq 42$  days after surgery (Table 2).



**Fig. 1.** Funnel plot with percentage radiotherapy  $\leq 42$  days after surgery, for breast cancer patients by hospital.

**Table 1B**  
Hospital and RTC characteristics.

	≤42 days, n = 10,790 (%)	>42 days, n = 5171(%)	P-value	≤42 days n = 4548 (%)	>42 days n = 1947(%)	P-value
<b>Type of hospital</b>						
General Hospital	5201 (48.2)	2556 (49.4)	0.298	2235 (49.1)	948 (48.7)	0.273
Top clinical Hospital	4588 (42.5)	2160 (41.8)		1873 (41.2)	832 (42.7)	
Academic Hospital	1001 (9.3)	455 (8.8)		440 (9.7)	167 (8.6)	
<b>Hospital surgical volume</b>						
<100	1651 (15.3)	766 (14.8)	0.363	713 (15.7)	307 (15.8)	0.974
100–200	4551 (42.2)	2241 (43.4)		1964 (43.2)	845 (43.4)	
>200	4588 (42.5)	2164 (41.8)		1871 (41.1)	795 (40.8)	
<b>Hospital of radiotherapy facilities</b>						
No RT facilities	7174 (66.5)	3697 (71.5)	<0.001	3068 (67.5)	1444 (74.2)	<0.001
On-site RT facilities	3616 (33.5)	1474 (28.5)		1480 (32.5)	503 (25.8)	
<b>Type of radiotherapy centre</b>						
Department of Academic Hospital	4630 (43.0)	2641 (51.1)	<0.001	1947 (42.8)	995 (51.1)	<0.001
Department of Top clinical Hospital	2562 (23.7)	1279 (24.7)		1081 (23.8)	439 (22.6)	
Independent centre	3598 (33.3)	1251 (24.2)		1520 (33.4)	513 (26.3)	

### Radiotherapy centres

About 46% of the patients had radiotherapy in a radiotherapy department of an academic hospital (Table 1B).

Within the same RTC, there was a large variance in time to start radiotherapy amongst the hospitals (Fig. 2). For example, the radiotherapy department of academic hospital 'AC 2' had patients from a hospital where 13% received treatment ≤42 days (minimum) and patients from a hospital where 63% received treatment ≤42 days (maximum). The variation within

independent RTCs and departments of top clinical hospitals was comparable. The variation was largest for hospitals that referred patients to the radiotherapy department of an academic hospital (Fig. 2).

### Multilevel analysis

First, a null model was generated, revealing the variance at each level. The null model for the period 2009–2011, without any explanatory variables, showed that 11.0% of the variance could be

**Table 2**  
Multilevel logistic regression with odds ratios of having radiotherapy ≤42 days after surgery (2009–2011).

	Univariate logistic regression <sup>a</sup>		Multivariable logistic regression <sup>b</sup>	
	OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Incidence year</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
2009	0.61 (0.56–0.66)		0.59(0.54–0.64)	
2010	0.97 (0.88–1.05)		0.92(0.84–1.01)	
2011	1		1	
<b>Age</b>		<0.001 <sup>a</sup>		0.014 <sup>b</sup>
<50	0.78 (0.71–0.87)		0.94 (0.84–1.04)	
50–59	1		1	
60–69	0.97 (0.88–1.06)		0.93 (0.85–1.02)	
70–79	0.84 (0.76–0.94)		0.85 (0.76–0.95)	
>80	0.54 (0.43–0.66)		0.75 (0.60–0.94)	
<b>Stage (pTNM)</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
DCIS	0.91 (0.81–1.02)		0.90 (0.80–1.01)	
I	1		1	
II	0.49 (0.45–0.54)		0.53 (0.48–0.58)	
III	0.32 (0.28–0.36)		0.44 (0.38–0.52)	
X	0.41 (0.20–0.85)		0.56 (0.27–1.18)	
<b>Type of surgery</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
Breast conserving surgery	1		1	
Mastectomy	0.40 (0.36–0.45)		0.66 (0.58–0.76)	
<b>Type of Hospital</b>		0.174		
General Hospital	1			
Top clinical Hospital	1.17 (0.93–1.48)			
Academic Hospital	1.33 (0.93–1.92)			
<b>Volume</b>		0.762		
<100	1.04 (0.80–1.36)			
100–200	1			
>200	1.11 (0.84–1.45)			
<b>Hospital radiotherapy facilities</b>		0.074 <sup>a</sup>		0.024 <sup>b</sup>
No RT facilities	1		1	
On-site RT facilities	1.26 (0.98–1.63)		1.36 (1.04–1.77)	
<b>Type of radiotherapy centre</b>		0.320		
Department of Academic Hospital	1			
Department of Top clinical Hospital	1.08 (0.52–2.25)			
Independent centre	1.69 (0.82–3.48)			

OR, odds ratio; 95% CI, 95% confidence interval; RT, radiotherapy.

<sup>a</sup> Threshold P < 0.10.

<sup>b</sup> Statistically significant (P < 0.05).

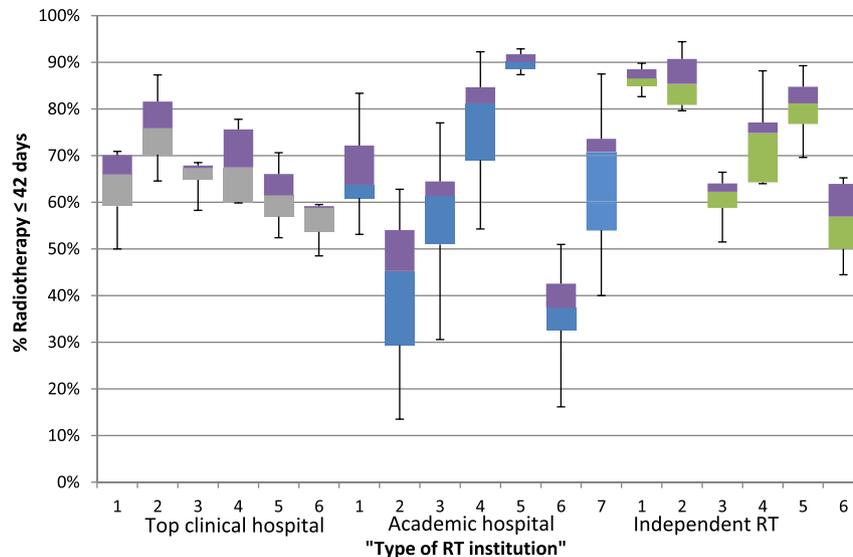


Fig. 2. Box plots with percentage radiotherapy  $\leq 42$  days after surgery for hospitals by RTCs.

attributed to the RTC level and 6.7% to the hospital level. Both the variance of the hospital level and the variance of the RTC level were statistically significant ( $\sigma^2 = 0.247$ , SE 0.053;  $\sigma^2 = 0.435$ , SE 0.159). Table 2 shows the results of the univariate analysis and multivariable analysis for 2009–2011.

In the null model for 2011, of the total variances, 8.6% ( $\sigma^2 = 0.338$ , SE 0.142) were at the RTC level, and 8.0% ( $\sigma^2 = 0.317$ , SE 0.083) at hospital level. Variances on both levels were statistically significant. Table 3 shows the results of the univariate analysis and multivariable analysis for 2011.

#### Patient factors

In the univariate model for 2009–2011 (Table 2), incidence year, age, stage and type of surgery were associated with radiotherapy  $\leq 42$  days. In the multivariate model, these variables remained significant. Compared to cases diagnosed in 2011, patients diagnosed in 2009 were less likely to receive radiotherapy  $\leq 42$  days after surgery (OR 0.59, 95% CI 0.54–0.64). Patients older than 80 years (OR 0.75, 95% CI 0.60–0.94), patients with advanced stage III (OR 0.44, 95% CI 0.38–0.52), and patients who underwent mastectomy (OR 0.66, 95% CI 0.58–0.76), were significantly less likely to receive radiotherapy  $\leq 42$  days after surgery.

Additional analysis for patients in 2011 (Table 3) shows that, besides the variables mentioned above, multifocality, ASA category, type of radiotherapy and palpability were associated with radiotherapy  $\leq 42$  days after surgery in the univariate model. In the multivariate model, the ASA category remained significant. Patients with ASA category 3 were less likely to receive radiotherapy  $\leq 42$  days after surgery (OR 0.57, 95% CI 0.43–0.74). Patient factors including age, stage and type of surgery also remained factors with significant influence on the likelihood of receiving radiotherapy  $\leq 42$  days after surgery. This was comparable to the results of the multivariable analysis of the data of 2009–2011.

#### Hospital factors

Of the hospital factors, only availability of radiotherapy facilities was associated with radiotherapy time interval in the univariate model ( $p = 0.074$ ). In the multivariable analyses, this variable remained significant when adjusted for other factors. Patients who underwent surgery in hospitals with on-site radiotherapy facilities were more likely to have radiotherapy  $\leq 42$  days compared to

patients treated in hospitals without radiotherapy facilities (OR 1.36, 95% CI 1.04–1.77).

#### RTC factors

In univariate analysis, the type of RTC had no significant effect on the time interval of receiving radiotherapy after surgery ( $p = 0.320$ ).

#### Multilevel analyses full model

Including the significant patient and hospital factors into the full model (Table 2), the factors significantly associated with the time interval between radiotherapy and surgery were year of incidence, age, stage, type of surgery, ASA category and availability of radiotherapy facilities. Of the remaining variation, significant unexplained variation was at the RTC level (11.1%,  $\sigma^2 = 0.254$ , SE 0.054) and the hospital level (6.4%  $\sigma^2 = 0.443$ , SE 0.163) (ICC 0.064). This unexplained variation indicates as yet undefined factors at hospital and RTC level.

#### Discussion

This population-based study in the Netherlands among 79 hospitals and 19 RTCs shows a large inter-hospital and inter-RTC variation in the time interval between surgery and start of radiotherapy in BC patients in the period 2009–2011. This study examined the factors that influence the indicator timing of adjuvant radiotherapy set by NABON: the percentage of patients receiving radiotherapy  $\leq 42$  days after surgery. In 68% of the patients in our study ( $n = 15,961$ ), this was achieved. An increase in the percentage was observed over the years, from 61% in 2009 to 70% in 2011. This improvement over time is likely to be the result of the actions enabling transparency, particularly with respect to waiting times [15]. In 90% of the patients, radiotherapy started  $\leq 56$  days. This corresponds well with the international guideline of EUSOMA, which recommends that patients without chemotherapy receive radiotherapy within 8 weeks [16]. The variances between hospitals and RTCs found in this study are in line with previous reports [17–19].

Several factors at patient, hospital and RTC level influenced whether patients received radiotherapy  $\leq 42$  days. The patient factors stage and type of surgery were found to be most dominant

**Table 3**  
Multilevel logistic regression with odds ratios of having radiotherapy  $\leq 42$  days after surgery (2011).

	Univariate logistic regression <sup>a</sup>	P-Value	Multivariable logistic regression <sup>b</sup>	P-Value
	OR (95% CI)		OR (95% CI)	
<b>Age</b>		<0.001 <sup>a</sup>		0.023 <sup>b</sup>
<50	0.73 (0.62–0.86)		0.84 (0.70–1.00)	
50–59	1		1	
60–69	0.96 (0.82–1.12)		0.95 (0.81–1.12)	
70–79	0.73 (0.61–0.86)		0.79 (0.66–0.94)	
>80	0.45 (0.33–0.61)		0.69 (0.50–0.96)	
<b>Stage (pTNM)</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
DCIS	0.85 (0.71–1.03)		0.85 (0.70–1.03)	
I	1		1	
II	0.53 (0.46–0.61)		0.58 (0.49–0.67)	
III	0.27 (0.22–0.32)		0.37 (0.28–0.50)	
X	0.36 (0.10–1.34)		0.39 (0.10–1.47)	
<b>Multifocal</b>		<0.001 <sup>a</sup>		0.386
No	1		1	
Yes	0.61 (0.51–0.74)		0.91 (0.75–1.12)	
<b>ASA category</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
1	1		1	
2	0.84 (0.73–0.96)		0.88 (0.76–1.02)	
3	0.48 (0.37–0.61)		0.57 (0.43–0.74)	
Unknown	0.90 (0.72–1.13)		1.00 (0.79–1.27)	
<b>Palpability</b>		<0.001 <sup>a</sup>		0.332
No	1		1	
Yes	0.73 (0.65–0.82)		1.08 (0.94–1.25)	
Unknown	0.72 (0.50–1.05)		0.85 (0.58–1.26)	
<b>Type of surgery</b>		<0.001 <sup>a</sup>		<0.001 <sup>b</sup>
Breast conserving surgery	1		1	
Mastectomy	0.34 (0.29–0.40)		0.54 (0.42–0.70)	
<b>Type of radiotherapy</b>		<0.001 <sup>a</sup>		0.144
Breast/chest wall with boost	1		1	
Breast/chest wall without boost	0.89 (0.78–1.02)		1.07 (0.92–1.24)	
Breast/chest wall + with boost regional	0.69 (0.53–0.90)		1.10 (0.83–1.47)	
Breast/chest wall + without boost regional	0.45 (0.37–0.56)		1.52 (1.13–2.03)	
Other	0.31 (0.10–1.03)		0.91 (0.26–3.14)	
Unknown	0.79 (0.53–1.18)		1.16 (0.76–1.76)	
<b>Type of hospital</b>		0.604		
General Hospital	1		1	
Top clinical Hospital	1.00 (0.74–1.34)		1.00 (0.74–1.34)	
Academic Hospital	1.26 (0.79–2.01)		1.26 (0.79–2.01)	
<b>Volume</b>		0.759		
<100	1.01 (0.72–1.41)		1.01 (0.72–1.41)	
100–200	1		1	
>200	1.13 (0.81–1.57)		1.13 (0.81–1.57)	
<b>Hospital radiotherapy facilities</b>		0.019 <sup>b</sup>		0.011 <sup>b</sup>
No RT facilities	1		1	
On-site RT facilities	1.44 (1.06–1.96)		1.52 (1.10–2.10)	
<b>Type of radiotherapy centre</b>		0.651		
Department of Academic Hospital	1		1	
Department of Top clinical Hospital	1.01 (0.50–2.07)		1.01 (0.50–2.07)	
Independent centre	1.35 (0.68–2.70)		1.35 (0.68–2.70)	

OR, odds ratio; 95% CI, 95% confidence interval; RT, radiotherapy.

<sup>a</sup> Threshold  $P < 0.10$ .

<sup>b</sup> Statistically significant ( $P < 0.05$ ).

factors on patient level. Patients with pathological stage II and III disease waited longer to receive radiotherapy than patients with stage I. This latter finding corresponds with those of another population-based study in which the investigators found shorter waiting times for patients with stage I [20]. Patients who underwent mastectomy were more likely to receive radiotherapy  $>42$  days after surgery. This may be due to differences in post-surgery complications and a longer recuperation time of mastectomy. As in Bouche et al. [21], a significant lower likelihood of older patients receiving radiotherapy  $\leq 42$  days was found. This corresponds with Struikmans et al. [4], who found that increasing age was associated with a reduced use of radiotherapy.

Overall, this study reveals a large variation in time to start radiotherapy among hospitals and RTCs. Patients who underwent

surgery in hospitals with on-site radiotherapy facilities, irrespective of the type of operating hospital, were more likely to receive radiotherapy  $\leq 42$  days after surgery. The largest variation was between hospitals that referred patients to the radiotherapy department of an academic hospital. After adjustment in the multivariable analysis for patient factors and hospital factors, variation between hospitals and RTCs remained significant, suggesting an influence of both hospitals and RTCs. This unexplained variance at hospital and RTC level indicates that there may be other factors that were not taken into account in this study, and this requires additional research.

An important factor for variation in timing is likely to be the differences in organization of care between hospital and RTCs. At RTC level, the time interval between surgery and start of

radiotherapy is not fully explained by the type of centre. In Ash [22], the major contributors to delay on RTC level were limitations in capacity, and Van Lent et al. [23] found that several factors could be associated with longer time intervals: high workload (patients treated per staff member), long access times and a high number of patients treated per linear accelerator (per standard working hour). Since there are different working strategies for RTCs in the Netherlands, strategies concerning information transfer and scheduling procedures, this may influence waiting times. In the Netherlands, some patients are invited based on the planned date of operation, some immediately after the tumour board, which is mandatory for all BC patients in the Netherlands, and, in other cases, the departments await a formal referral with complete documentation. On the basis of our study, further research should examine in detail the effect of capacity, workload and information transfer on waiting times.

At hospital level, the organization of tumour boards may influence the time interval through sequences in pre-treatment imaging and consultation with other specialists [24]. For example, in Dutch hospitals there are differences in the frequencies of the meetings of the tumour boards. These can vary from between twice a week with a special board for BC only, to once a week for all tumours. In addition, in some hospitals without on-site radiotherapy facilities, radiotherapy consults are available in the outpatient department. Further research is needed to explore whether information transfer and scheduling patients are better organized in these situations, and how this influences the timing of radiotherapy.

Published evidence about the optimal time interval and treatment efficacy is contradictory. Some studies have shown that patients with longer waiting times for radiotherapy have an increased risk of local recurrence [25–27]. However, Livi et al. [28] note that timing of radiotherapy itself does not affect local recurrence, but prognostic factors do. A corresponding study by Jobsen et al. [29] found that a time interval of more than 112 days had no negative effect on local control. In another study, Jobsen et al. [30], found a significant negative effect for survival in starting radiotherapy shortly after surgery (1–36 days) and survival benefit for starting radiotherapy after 36 days for patients with breast conserving surgery ( $n = 1473$ ). Besides, interaction between combinations of therapies could confound the effect of delay in radiotherapy.

The present study has a number of strengths and limitations. The main strength lies in the large size of the study population for which data was complete and gathered from patient files in a standardized manner. Another strength of this study is that information was collected at patient, hospital and RTC level. It was therefore possible to examine the share of each level of the total variance, and which factors at each level were related to the start of adjuvant radiotherapy  $\leq 42$  days after surgery. The study is, however, limited, especially at RTC level, because the availability of detailed explanatory RTC factors was limited. It was therefore unable to explain which factors influenced the variance on RTC level. On the other hand, this study provides clear insight into the variation in timing amongst hospitals and RTCs, and provides data useful for analysing time intervals in further studies.

In conclusion, this population based study reports large variations in time between surgery and start of adjuvant radiotherapy between hospitals and RTCs in BC patients in the Netherlands. After adjustment of patient factors and hospital factors, unexplained variance on RTC and hospital level remained significant. This suggests delays caused by the patient referral pathway from hospital to RCT, and indicates possibilities for improvement. Further research should examine underlying causes at both hospital and RCT level.

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## Conflict of interest statement

Authors declare that they have no conflict of interest.

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