IKNL integraal kankercentrum Nederland

Variation in the use of ultra-hypofractionated irradiation in breast cancer in the Netherlands during the COVID-19pandemic

Master thesis

Eva J.A. van Beek

2023-2024

Supervisors: Prof. dr. Sabine Siesling &
Dr. Anouk H. Eijkelboom
Faculty: Science and Technology
Study: Health Sciences (HS)

June 28, 2024

Abstract

Purpose

Follow-up studies supporting the use of ultra-hypofractionated radiotherapy schemes, along with international COVID-19 guidelines indicating the implementation of these schemes and the first COVID-19 cases in the Netherlands in 2020 brought the ultra-hypofractionated schemes to attention. However, the extent of the implementation of these schemes in the Netherlands is unclear. This study aims to investigate the variation in the use of irradiation schemes, including the implementation of ultra-hypofractionated schemes and the factors influencing the chance of receiving ultra-hypofractionated radiotherapy. In addition, the reasoning behind radiotherapy institutions' decisions to implement ultra-hypofractionated schemes in specific cases was investigated.

Methods

Non-metastatic, female patients with invasive breast cancer or DCIS, 18 years and older, who received postoperative RT between January 2020 and December 2021 and who were registered in the Netherlands Cancer Registry and the NABON Breast Cancer Audit Radiotherapy were included. Data analysis for 9599 tumours was done to determine the implementation of the RT schemes over time, logistic regression was used to determine which factors were associated with the implementation of ultra-hypofractionated schemes. A questionnaire was distributed among all Dutch radiotherapy institutes (n=19) to determine the reasoning of these institutes behind the implementation of the ultra-hypofractionated schemes.

Results

In 2021, the ultra-hypofractionated schemes were implemented to a larger extent and with more variation between radiotherapy institutes compared to 2020. According to the data analysis and questionnaire, at the start of the COVID-19 pandemic in the Netherlands, the ultra-hypofractionated schemes peaked in use, especially the 5x5.2 Gy (with 42 patients in April 2020) and the 5x5.7 Gy (with 55 patients in May 2020) schemes. These peaks were due to the institutions' desire to reduce the pressure on healthcare and to prevent infections. From June 2020, the 5x5.2 Gy scheme increased in use and from March 2021 the 5x5.7 Gy scheme decreased. The patient's age, tumour size, lymph node involvement, type of RT centre, PBI treatment and the period of administration were significantly associated with the implementation of ultra-hypofractionated schemes (5x5.2 Gy, 5x5.7 Gy, 5x6 Gy) according to the logistic regression. Most indicated factors influencing the implementation of these schemes according to the questionnaire were dosimetric homogeneity, wound (healing) problems and (large) seromas.

Conclusion

The use of ultra-hypofractionated schemes, especially the 5x5.2 and 5x5.7 Gy schemes, has increased for non-metastatic surgically treated breast cancer patients after March 2020. Low-risk patients, university-related RT institutes, PBI treatment, the start of the COVID-19 pandemic and the LPRM meetings were influencing factors on whether to implement the ultra-hypofractionated schemes. The RT institutes indicated that (large) seromas, wound problems and dosimetric inhomogeneity were frequently answered factors not to implement the schemes.

Contents

1 Introduction

Breast cancer is the most common cancer type for women in the Netherlands, with an incidence rate of around 18.000 women in 2022 [1]. Post-operative radiotherapy (RT) is used in around 97.3% of patients with non-metastatic invasive breast cancer after breast-conserving surgery (BCS) and without primary systemic therapy (PST). After a mastectomy, it is used for only 26.1% of these patients. The aim of RT is to reduce both locoregional recurrence rates and mortality rates [2,3].

Adjuvant RT in breast cancer consists of a total irradiation dose delivered to the patient in a certain number of fractions. In conventional methods, patients received lower doses per fraction: 25 fractions with 2 Gray (Gy) per fraction [4,5]. An additional irradiation dose to the breast tissue where the primary tumour is located is often given, called a boost [6]. A boost of approximately 16 Gy can be used to enhance local control rates in BCS [4]. In later years, several studies showed that increasing the dose per fraction and reducing the number of fractions, which is called hypofractionated RT (15x2.67 Gy [5,7,8]), had a similar or improved effect on the breast cancer outcomes compared to conventional method [5,7–11]. Examples of these outcomes were locoregional recurrence rates [7–11], overall survival [9–11], cosmetic outcomes [8,9,11] and long-term toxic effects [12]. By decreasing the number of fractions, the number of visits to the RT department can be reduced. This could result, for example, in shorter waiting times and improved patient compliance [13].

In April and July of 2020 (Figure 1), the results of two follow-up studies of randomised control trials were published, providing insights into the effects of five fraction RT schemes, which are called ultra-hypofractionated RT [14,15]. The FAST-Forward trial showed that adjuvant RT with 26 Gy in five once-daily fractions was noninferior to 40 Gy in 15 fractions in terms of local tumour control. The newer irradiation schedule was also safe for the patients in terms of normal tissue effects for up to five years [14]. The second study presented the result of the FAST trial after 10 years of follow-up. This trial investigated the effects of five once-weekly fractions of 30 Gy (6 Gy per fraction) and 28.5 Gy (5.7 Gy per fraction) versus 50 Gy in 25 fractions. Using 28.5 Gy in 5 once-weekly fractions was non-inferior to 50 Gy in 25 fractions in terms of normal tissue effects in the breast [15]. Furthermore, in August 2020, the long-term results of the Florence trial were published. This trial compared the APBI 5x6 Gy scheme using intensity-modulated RT with the conventional method (25x2 Gy) for WBI, using ipsilateral breast tumour recurrences (IBTR). IBTR had an insignificant difference between the two schemes and the APBI arm had significantly better outcomes in terms of late toxicity and cosmetic outcomes than the WBI arm [16].

In February 2020, a few months before the publications of the FAST and FAST-Forward trials, the first cases of COVID-19 were identified in the Netherlands [17]. Measures and guidelines were introduced in breast cancer care to minimize the infection of COVID-19 for both patients and healthcare professionals and to reduce the burden on care in case of limited resources. One of the international recommendations was to implement the five fraction irradiation schemes, like in the FAST and FAST-Forward trials, for patients with node-negative tumours not requiring a boost [18]. Furthermore, in November 2020 and April 2021, the NVRO (Dutch Society of Radiology and Oncology) organised the LPRM (National Platform Radiotherapy Breast Cancer) meetings that introduced national recommendations for the implementation of ultra-hypofractionated schemes. The recommendations brought the ultra-hypofractionated irradiation schemes to the attention of the RT departments in the Netherlands. This increased attention during the pandemic and the benefits and evidence of the ultra-hypofractionated irradiation schemes might have enhanced the implementation of these schemes. However, it is unclear to what extent these schemes or other irradiation schemes have been used in breast cancer care in the Netherlands during the COVID-19 pandemic. Understanding this could reveal how RT schemes are constantly evolving to be more efficient. Therefore, the aim of this study was to determine: the variation in the use of irradiation schemes in the Netherlands during COVID-19 (2020-2021); the implementation of ultra-hypofractionated RT schemes during the COVID-19 pandemic (2020-2021); the current reasoning behind RT institutes' decisions to use ultra-hypofractionated schemes to specific cases; the factors influencing the chance of receiving ultra-hypofractionated RT during the COVID-19 pandemic (2020-2021).

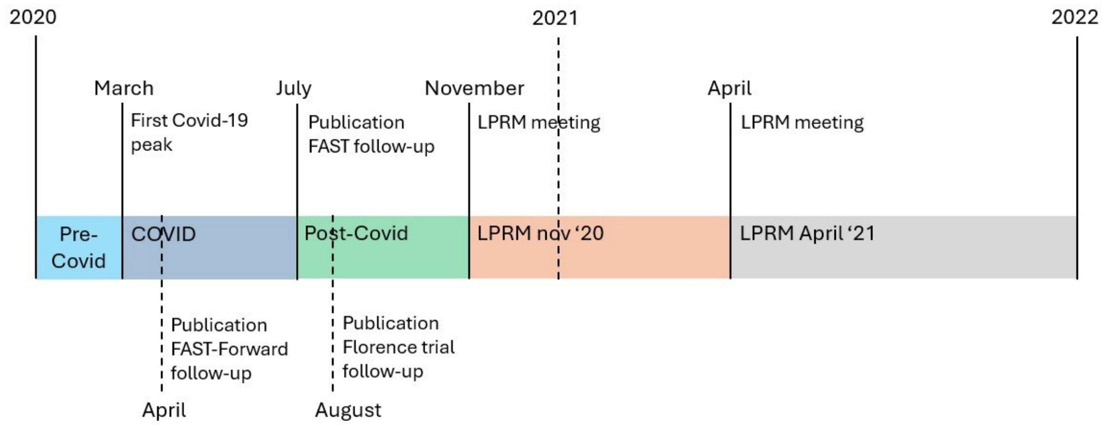

Figure 1: Timeline of noticeable events and periods during 2020 and 2021.

2 Methods

In this study, a mixed-method approach was used, consisting of data analysis and a questionnaire. Patient data from Dutch RT institutes was analysed to determine the variation over time in the implementation of RT schemes and investigate the difference in the use of ultra-hypofractionated RT schemes between RT departments. In addition, the data was used to identify influencing factors (patient, tumour, RT treatment and time periods) for using five fractions. The questionnaire was distributed among Dutch radiotherapy (RT) institutes to get an overview of the use and opinions of the 5x5.2 Gy scheme and partly the 5x5.7 Gy scheme.

2.1 Data collection

Data on the RT treatment, periods, tumour and patient characteristics of breast cancer patients was collected by linking data from the Netherlands Cancer Registry (NCR) and the NABON Breast Cancer Audit Radiotherapy (NBCA-R) from 12 out of 19 Dutch RT institutes. NBCA-R is an extension of the NBCA, focusing on patients who have received radiotherapy. It includes information about the irradiation dose, number of fractions and boost information. The NBCA-R was an initiative of the Netherlands Association for Radiotherapy and Oncology (NVRO) in 2020, to register radiotherapy data and is registered by radiotherapy departments in the Netherlands. The NCR data is hosted by the Netherlands Comprehensive Cancer Registry (IKNL). The data is collected by specially trained data managers from the NCR. This data includes patient characteristics (e.g. gender, socioeconomic status), tumour characteristics (e.g. tumour type, tumour size) and treatment information (e.g. most extensive surgery, incidence date).

2.2 Study population

Non-metastatic, female patients with either stage I, II or III of invasive BC or DCIS (TNM staging system), 18 years and older, who had received postoperative RT between January 2020 and December 2021 were included in this study. A patient may appear more than once in the data set because a different tumour diagnosis for the same patient was considered as a separate treatment path. Whether a patient had local recurrence is not registered in the NCR, however, the RT treatment registered in the NBCA-R could be for a recurrence. For patients who were considered to have had local recurrence, the recurrent treatment was excluded. Patients were excluded if: the NCR and NBCA-R data about the start date of the RT were both missing and the patient did not receive RT according to the NCR; the difference between the start date of the RT of NCR and NBCA-R was more than one month and the difference between the start of RT and the incidence date of the tumour was more than 386 days (99% interval); and the difference between the start date of the RT and the incidence date was more than 386 days (99% interval) and the NCR did not register that the patient received radiotherapy.

2.3 Statistical analysis

The baseline characteristics of the included patients were discussed descriptively and visualised in four categories. These categories consist of the two most common irradiation schemes (15x2.67 Gy, 20x2.18 Gy including 15x2.67 Gy fractions with a sequential five fraction boost), the ultra-hypofractionated schemes (5x5.2 Gy, 5x5.7 Gy, 5x6 Gy, 5x5.4 Gy, 5x5.67 Gy) and the category "other" including the less common schemes (10x3.85 Gy, 22x2.03 Gy, 25x2 Gy, 23x2 Gy or 23x2.03 Gy). These categories were also used for the visualisation of the variation in the use of the RT schemes over the months of 2020-2021. Furthermore, the variation in the number of patients for the specific ultra-hypofractionated schemes was also visualised with the three most used schemes: 5x5.2 Gy, 5x5.7 Gy and 5x6 Gy. Boxplots were constructed to compare the implementation of all five fraction schemes together between RT institutes for the years 2020 and 2021. The number of patients that received five fractions within RT institutes was expressed as a percentage of all patients treated with RT, these percentages were compared.

Logistic regression was used to determine the odds ratios and the 95% confidence intervals for influencing factors on the implementation of ultra-hypofractionated RT. The original data had missing values in the variables socioeconomic status (SES), lymph node involvement, tumour size, travel time (to RT location by car) and PBI treatment. Imputation was executed using Multiple Imputation by Chained Equations (MICE) [19,20] using the variables from the logistic regression (listed below). The logistic regression was done for the periods 2020 and 2021 separately to divide the first COVID-19 peak and measures (in 2020) and the more acclimated period following these peaks and first recommendations (in 2021). In addition, 2020 and 2021 were analysed together to get an overview of the study period. The following patient factors were entered into the model: age (<50, 50-54, 55-59, 60-64, 65-69, 70-74, 75≥), SES (low, medium, high), travel time from patients' postal code to RT location by car (0-9, 10-19, 20-29, 30≥ minutes). Furthermore, the following tumour characteristics were analysed: tumour type (invasive with DCIS component, without DCIS component and DCIS), involvement of lymph nodes (yes, no) and tumour size (0-9, 10-19, 20-29, 30≥ mm). In addition, the following RT treatment factors were included: type of RT department (hospital, university, independent) and Partial Breast Irradiation (PBI) treatment (yes, no). Lastly, noteworthy periods following important events during 2020 and 2021 were analysed (pre-Covid, first COVID peak from March 2020 to June 2020, post-Covid and LPRM meetings in November 2020 and April 2021). The logistic regression was done with both univariate and multivariate analysis. The factors were considered significant with a p-value <0.05. The data from the NBCA-R and NCR was analysed using Stata Software (version 17, StataCorp, Texas, USA).

2.4 Questionnaire

The questionnaire was developed using Qualtrics XM and distributed among all RT departments in the Netherlands (n=19). The questionnaire consisted of general questions (i.e. target volumes), patient-related questions (e.g. age) and toxicity questions about the 5x5.2 Gy scheme. For example, a question about whether a bolus, a tissue equivalent material that moves the irradiation dose to the skin [21,22], influences the decision of using 5x5.2 Gy. In addition, non-patient-related questions (e.g. impact of COVID-19 on the implementation of ultra-hypofractionated schemes) were included for both the 5x5.2 Gy and the 5x5.7 Gy schemes. See Appendix A for all questions and answer options. The answers to the questions were individually analysed and the results were discussed descriptively or visualised using horizontal bar graphs.

3 Results

3.1 Study population

In 2020 and 2021, a total of 9599 tumours in a total of 9505 patients were included from 12 RT institutes (63.16%) out of all 19 institutes in the Netherlands. Figure 2 shows an overview of the included study population with the exclusion criteria and the number of excluded patients.

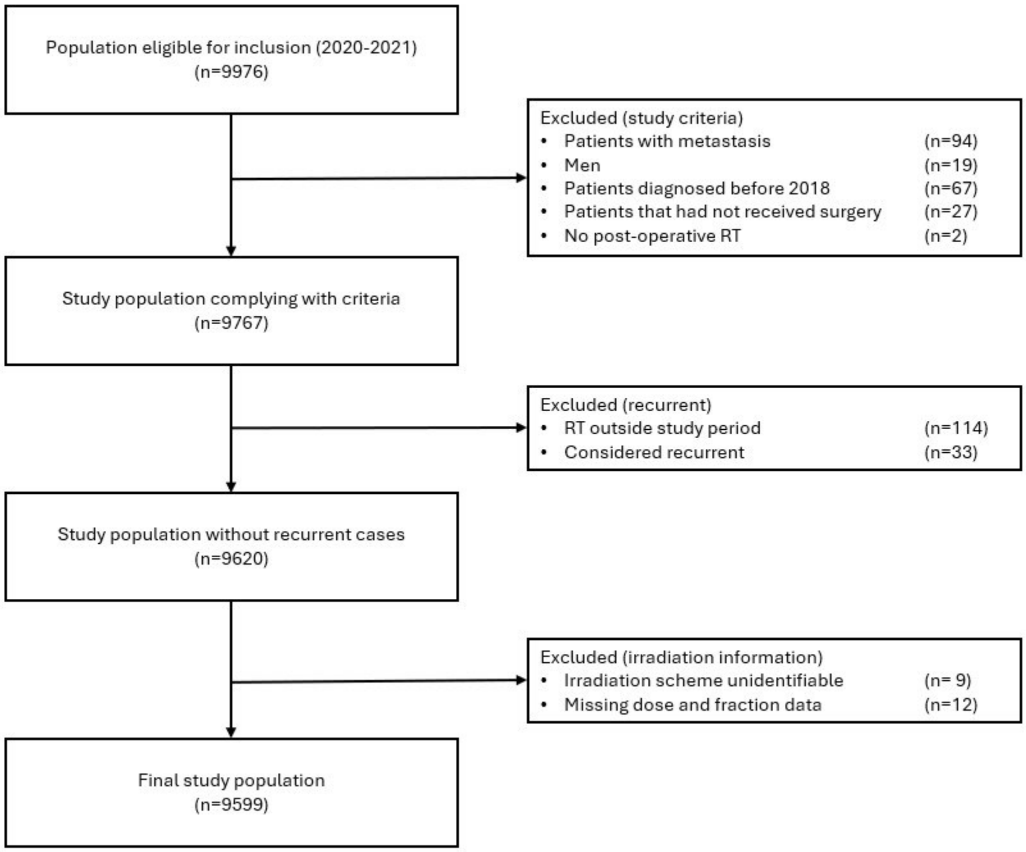

Figure 2: Overview of the study population with the exclusion criteria.

The patient, tumour, RT treatment and time characteristics are visible in Table 1. These characteristics were divided by the general RT schemes: 5 fractions, 15 fractions, 20 fractions and "other" schemes. These groups consist of 1548 patients, 5436 patients, 2487 patients and 128 patients respectively. There is a higher percentage of older patients included in the five fraction scheme compared to all other schemes combined. Furthermore, the five fraction schemes included a higher percentage of pT1 tumours without lymph node involvement. In addition, patients receiving five fractions were more often irradiated in university-related RT centres and with PBI compared to patients receiving another RT schedule.

Table 1: Baseline characteristics by RT scheme. Indicating the number of tumours and percentage for 5 fractions, 15 fractions, 20 fractions and "other" fractions.

	Subgroup	5 fractions	15 fractions	20 fractions	Other
Included tumours		1548	5436	2487	128
Age	$\leq$ 50	119 (7.69%)	910 (16.74%)	751 (30.20%)	15 (11.72%)
	50-54	230 (14.86%)	780 (14.35%)	364 (14.64%)	14 (10.94%)
	55-59	169 (10.92%)	746 (13.72%)	327 (13.15%)	13 (10.16%)
	60-64	246 (15.89%)	792 (14.57%)	288 (11.58%)	18 (14.06%)
	65-69	289 (18.67%)	818 (15.05%)	328 (13.19%)	26 (20.31%)
	70-74	289 (18.67%)	770 (14.16%)	242 (9.73%)	20 (15.63%)
	75 $\geq$	206 (13.31%)	620 (11.41%)	187 (7.52%)	22 (17.19%)
SES	Low	342 (22.09%)	1266 (23.29%)	572 (23%))	27 (21.09%)
	Medium	530 (34.24%)	1967 (36.18%)	942 (37.88%)	53 (41.41%)
	High	633 (40.89%)	2074 (38.15%)	922 (37.07%)	47 (36.72%)
	Unknown	43 (2.78%)	129 (2.37%)	51 (2.05%)	1 (0.78%)
Travel time (minutes)[a]	$\leq$ 10	225 (14.53%)	726 (13.36%)	333 (13.39%)	8 (6.25%)
	10-19	572 (36.95%)	1847 (33.98%)	846 (34.02%)	57 (44.53%)
	20-29	456 (29.46%)	1824 (33.55%)	853 (34.30%)	41 (32.03%)
	30 $\geq$	293 (18.93%)	1029 (18.93%)	452 (18.18%)	22 (17.19%)
	Unknown	2 (0.13%)	10 (0.18%)	3 (0.12%)	n.a.
Tumour type	Invasive with DCIS	651 (42.05%)	2399 (44.13%)	1197 (48.13%)	53 (41.41%)
	Invasive without DCIS	765 (49.42%)	2682 (49.34%)	1050 (42.22%)	71 (55.47%)
	DCIS	132 (8.53%)	355 (6.53%)	240 (9.65%)	4 (3.13%)
pT	0	83 (5.36%)	523 (9.62%)	179 (7.20%)	3 (2.34%)
	1	1137 (73.45%)	2934 (53.97%)	1450 (58.30%)	82 (64.06%)
	2	170 (10.98%)	1232 (22.66%)	517 (20.79%)	28 (21.88%)
	3	9 (0.58%)	245 (4.51%)	40 (1.61%)	7 (5.47%)
	4	3 (0.19%)	31 (0.57%)	8 (0.32%)	3 (2.34%)
	IS	137 (8.85%)	432 (7.95%)	282 (11.34%)	4 (3.13%)
	Unknown	9 (0.58%)	39 (0.72%)	11 (0.44%)	1 (0.78%)
Lymph node involvement	No	1373 (88.70%)	3302 (60.74%)	1753 (70.49%)	80 (62.50%)
	Yes	78 (5.04%)	1907 (35.08%)	624 (25.09%)	42 (32.81%)

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Table 1: *Baseline characteristics by RT scheme. Indicating the number of tumours and percentage for 5 fractions, 15 fractions, 20 fractions and "other" fractions. (Continued)*

	Unknown	97 (6.27%)	227 (4.18%)	110 (4.42%)	6 (4.69%)
ER-stat	Negative	142 (9.17%)	674 (12.40%)	643 (25.85%)	16 (12.50%)
	Positive	1269 (81.98%)	4388 (80.72%)	1596 (64.17%)	108 (84.38%)
	Unknown	137 (8.85%)	374 (6.88%)	248 (9.97%)	4 (3.13%)
PR-stat	Negative	373 (24.10%)	1465 (26.95%)	906 (36.42%)	38 (29.69%)
	Positive	1038 (67.05%)	3594 (66.11%)	1332 (53.56%)	86 (67.19%)
	Unknown	137 (8.85%)	377 (6.93%)	249 (10.01%)	4 (3.13%)
Her2 stat	Negative	1297 (83.79%)	4315 (79.38%)	1902 (76.48%)	116 (90.63%)
	Positive	105 (6.78%)	670 (12.33%)	317 (12.75%)	7 (5.47%)
	Unknown	146 (9.43%)	451 (8.30%)	268 (10.78%)	5 (3.91%)
Size of tumour (mm)	0-9	533 (34.43%)	1503 (27.65%)	695 (27.95%)	29 (22.66%)
	10-19	730 (47.16%)	2006 (36.90%)	961 (38.64%)	55 (42.97%)
	20-29	172 (11.11 %)	859 (15.80%)	464 (18.66%)	18 (14.06%)
	30 ≥	62 (4%)	781 (14.37%)	255 (10.25%)	22 (17.19%)
	Unknown	51 (3.29%)	287 (5.28%)	112 (4.50%)	4 (3.13%)
Type RT centre	Independent	251 (16.21%)	2162 (39.77%)	735 (29.55%)	14 (10.94%)
	Hospital related	206 (13.31%)	991 (18.23%)	598 (24.05%)	85 (66.41%)
	University	1091 (70.48%)	2283 (42%)	1154 (46.40%)	29 (22.66%)
PBI treatment	no PBI	957 (61.82%)	5141 (94.57%)	2471 (99.36%)	66 (51.56%)
	PBI	551 (35.59%)	251 (4.62%)	0 (0%)	61 (47.66%)
	Unkown	40 (2.58%)	44 (0.81%)	16 (0.64%)	1 (0.78%)
Periods	Pre-Covid	10 (0.65%)	393 (7.23%)	217 (8.73%)	13 (10.16%)
	Covid	224 (14.47%)	801 (14.74%)	472 (18.98%)	32 (25%)
	Post-Covid	161 (10.40%)	770 (14.16%)	438 (17.61%)	18 (14.06%)
	LPRM Nov '20	336 (21.71%)	1221 (22.46%)	488 (19.62%)	32 (25%)
	LPRM Apr '21	817 (52.78%)	2251 (41.41%)	872 (35.06%)	33 (25.78%)

[a]*Travel time is the travel time by car from the patients' postal code to the RT institute.*

DCIS, Ductal Carcinoma in Situ; ES, estrogen; HER2, Human Epidermal Growth Factor receptor 2; LPRM, National Platform Radiotherapy Breast Cancer; PBI, Partial Breast Irradiation; PR, Progesteron; RT, Radiotherapy; SES, Socioeconomic status.

3.2 Use of general RT schemes

The RT schemes mostly used for breast cancer patients at the beginning of 2020 were 15 fractions and 20 fractions. In April 2020 a steep increase in the use of five fractions was visible (Figure 3). In June 2020 there was a decrease in the use of five fractions, followed by a slow increase until December 2021 (Figure 3). The 20 fraction scheme slowly decreased during the study period. The number of patients for the "other" group did not show any peaks or trends.

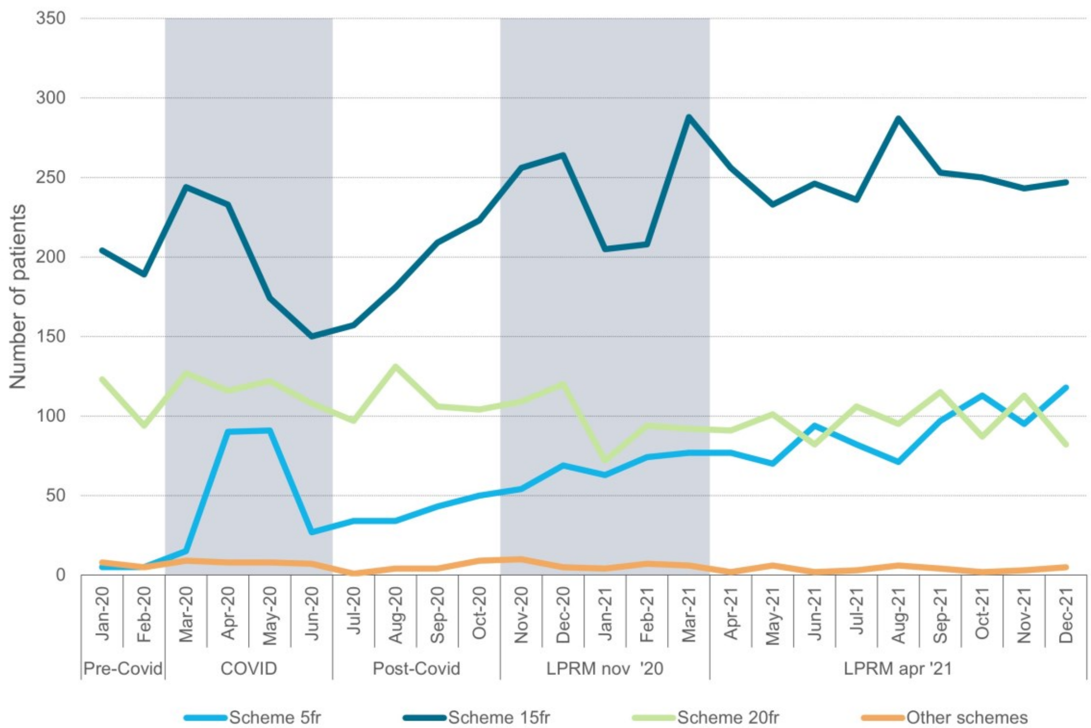

Figure 3: Increase of the implementation of RT per RT scheme over the periods in 2020-2021 by month. General schemes include 5 fractions, 15 fractions 20 fractions and "other" schemes. Fr = fractions.

3.3 Ultra-hypofractionated scheme

The use of the ultra-hypofractionated schemes (5x5.2 Gy, 5x5.7 Gy and 5x6 Gy) increased after March 2020 (Figure 4). The 5x5.2 Gy scheme peaked in April 2020 with 42 patients, after which the number dropped to only six in June. The 5x5.7 Gy (55 patients) and 5x6 Gy (8 patients) schemes peaked in May 2020 and fell afterwards. In July 2020, the use of 5x5.2 Gy started increasing while the 5x5.7 Gy and 5x6 Gy schemes remained lower. The use of 5x5.7 Gy increased slightly between December 2020 and February 2021 and decreased thereafter. From March 2021 the number of patients that received the 5x5.7 Gy scheme did not exceed five patients. The 5x6 Gy scheme was only used between March 2020 and February 2021 and was mainly used in combination with PBI and partly with irradiation on the breast/ thoracic wall without boost. Two small peaks were visible in May 2020 and December 2020.

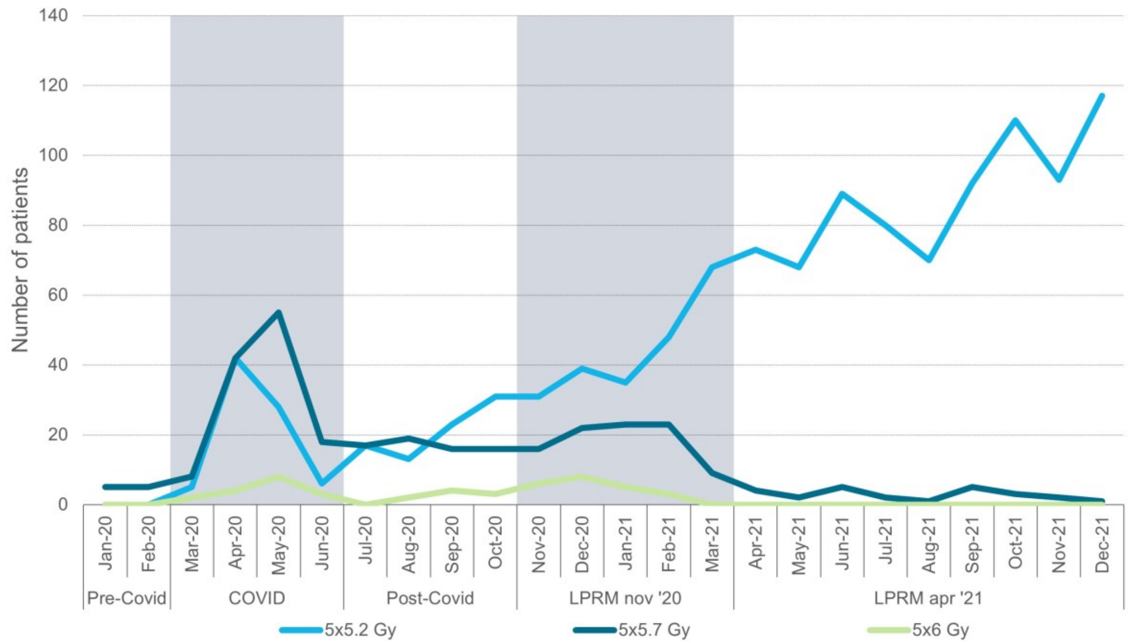

Figure 4: Use of specific five fraction schemes over the period 2020-2021 by month. The five fraction schemes include five fractions with 5.2 Gy per fraction, 5.7 Gy per fraction and 6 Gy per fraction.

Figure 5 compares the percentage use of five fractions between the RT institutes over 2020 and 2021. In 2021, the five fraction schemes were generally more implemented compared to 2020. In addition, more variability was visible between the RT institutes in 2021.

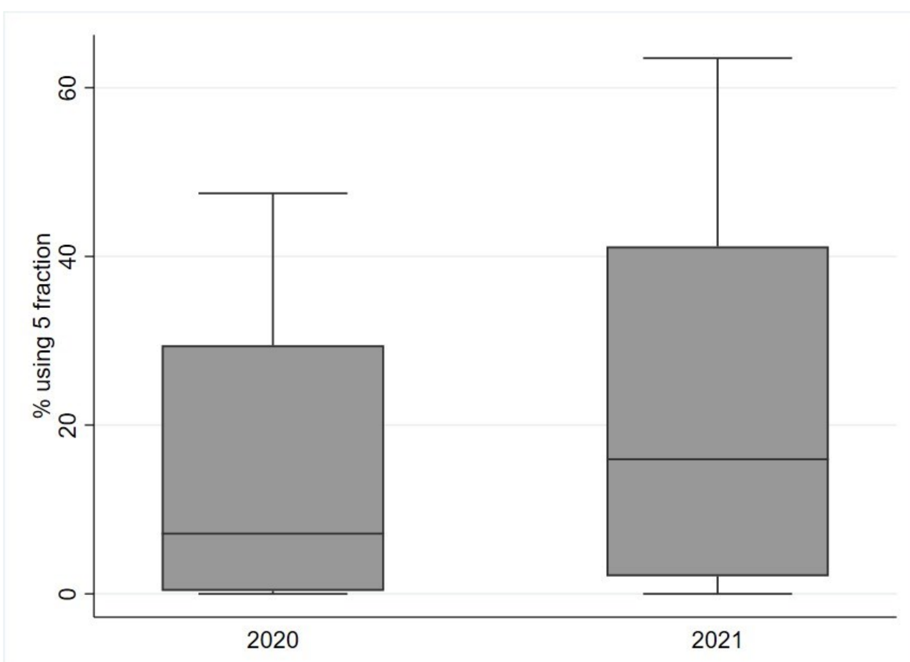

Figure 5: Variation of the percentage use of five fractions between RT institutes in 2020 and 2021.

3.3.1 Factors of influence

Older patients had significantly higher odds of receiving five fractions for both univariate and multivariate analyses in 2020-2021, 2020 and 2021 (Table 2). Other factors that caused significantly higher odds for tumours to be irradiated with five fractions in all three time periods were lymph node involvement, RT institute type and PBI treatment. In cases where there was no lymph node involvement, RT treatment at a university-related RT institute and PBI treatment, the chances of the tumour being irradiated with five fractions were also significantly higher. Furthermore, in 2020, patients irradiated in hospital-related RT institutes had lower odds of receiving five fraction schemes compared to those irradiated in independent RT institutes, in contrast to 2021 where patients irradiated in these institutes had higher odds than in independent RT institutes. In 2020-2021, hospital-related RT institutes were not a significant factor in the multivariate analysis.

For tumours irradiated in 2020-2021 and 2021, the size of the tumour was significantly associated with the administration of five fractions in univariate and multivariate analyses. Larger tumours (20 mm and bigger) had a significantly lower chance of irradiation with five fractions. In addition, the patients' travel time to the RT centre also had a significant influence. In 2021, patients travelling 0 to 9 minutes or 30 minutes or more had significantly higher odds of receiving five fractions than those travelling 20 to 29 minutes. In 2020-2021, patients travelling 0 to 9 minutes also had a significantly higher chance of receiving five fractions than those travelling 20 to 29 minutes.

Tumours irradiated with five fractions had significantly lower odds pre-Covid than post-Covid in both univariate and multivariate analyses, while the tumours irradiated in the COVID period had higher odds. Moreover, the odds of irradiation with five fractions after the LPRM meeting in April 2021 were higher. In addition, tumours irradiated after the LPRM in November 2020 had significantly higher odds of irradiation with five fractions than the post-Covid period according to the univariate analysis.

Table 2: The odds ratios and 95% confidence interval of receiving ultra-hypofractionated schemes. Univariate and multivariate analyses over the periods 2020-2021, 2020 and 2021.

	Years	2020-2021	2020-2021	2020	2020	2021	2021
Analysis		Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age	≤ 50	**0.46** (0.36-0.58)	**0.65** (0.49-0.86)	**0.5** (0.34-0.74)	0.67 (0.43-1.04)	**0.43** (0.32-0.59)	**0.64** (0.44-0.92)
	50-54	**1.28** (1.03-1.58)	1.29 (0.998-1.66)	1.28 (0.9-1.83)	1.34 (0.89-2.02)	1.25 (0.95-1.64)	1.27 (0.91-1.76)
	55-59	ref.	ref.	ref.	ref.	ref.	ref.
	60-64	**1.44** (1.16-1.78)	**1.3** (1.01-1.68)	1.25 (0.87-1.79)	1.18 (0.78-1.8)	**1.53** (1.17-1.99)	**1.4** (1.01-1.95)
	65-69	**1.58** (1.29-1.95)	**1.67** (1.31-2.13)	1.33 (0.94-1.9)	1.42 (0.95-2.13)	**1.7** (1.31-2.2)	**1.85** (1.35-2.53)
	70-74	**1.8** (1.46-2.22)	**2.07** (1.61-2.66)	**1.69** (1.2-2.38)	**1.76** (1.19-2.6)	**1.9** (1.46-2.48)	**2.39** (1.72-3.31)
	$75 \geq$	**1.6** (1.28-1.99)	**2.85** (2.17-3.74)	**1.55** (1.07-2.23)	**2.53** (1.65-3.88)	**1.65** (1.24-2.19)	**3.31** (2.3-4.75)
SES	Low	1.02 (0.88-1.19)	0.91 (0.76-1.09)	0.88 (0.69-1.14)	0.76 (0.56-1.01)	1.11 (0.92-1.34)	1.01 (0.8-1.28)

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Table 2: The odds ratios and 95% confidence interval of receiving ultra-hypofractionated schemes. Univariate and multivariate analyses over the periods 2020-2021, 2020 and 2021. (Continued)

	Medium	ref.	ref.	ref.	ref.	ref.	ref.
	High	**1.16** (1.02-1.31)	0.92 (0.79-1.07)	1.12 (0.9-1.38)	0.86 (0.68-1.11)	1.16 (0.99-1.36)	0.97 (0.79-1.18)
Travel time (minutes)[a]	0-9	**1.26** (1.06-1.5)	**1.28** (1.03-1.58)	1.18 (0.89-1.57)	0.99 (0.7-1.39)	**1.34** (1.08-1.68)	**1.51** (1.14-1.99)
	10-19	**1.24** (1.08-1.42)	1.06 (0.9-1.25)	1.08 (0.86-1.35)	0.92 (0.71-1.19)	**1.38** (1.17-1.64)	1.13 (0.91-1.39)
	20-29	ref.	ref.	ref.	ref.	ref.	ref.
	30 ≥	1.16 (0.99-1.36)	1.19 (0.98-1.45)	1.01 (0.77-1.34)	0.96 (0.7-1.33)	**1.23** (1.01-1.5)	**1.34** (1.05-1.72)
Tumour type	Invasive with DCIS	**0.89** (0.79-0.99)	0.93 (0.81-1.07)	0.94 (0.77-1.14)	1.01 (0.81-1.27)	**0.85** (0.74-0.99)	0.86 (0.72-1.03)
	Invasive without DCIS	ref.	ref.	ref.	ref.	ref.	ref.
	DCIS	1.1 (0.89-1.34)	0.99 (0.77-1.28)	**1.46** (1.06-2.02)	1.43 (0.98-2.1)	0.91 (0.7-1.18)	0.78 (0.56-1.09)
Lymph node involvement	No	ref.	ref.	ref.	ref.	ref.	ref.
	Yes	**0.12** (0.1-0.15)	**0.18** (0.14-0.23)	**0.17** (0.12-0.24)	**0.21** (0.14-0.3)	**0.1** (0.07-0.13)	**0.16** (0.11-0.22)
Tumour size (mm)	0-9	ref.	ref.	ref.	ref.	ref.	ref.
	10-19	1.01 (0.89-1.14)	0.95 (0.82-1.11)	0.99 (0.8-1.23)	1.03 (0.8-1.31)	1.02 (0.87-1.19)	0.91 (0.75-1.11)
	20-29	**0.54** (0.45-0.64)	**0.73** (0.59-0.91)	**0.54** (0.4-0.74)	0.74 (0.52-1.05)	**0.55** (0.43-0.69)	**0.72** (0.55-0.96)
	30 ≥	**0.24** (0.19-0.32)	**0.5** (0.37-0.67)	**0.37** (0.25-0.56)	0.76 (0.49-1.19)	**0.18** (0.12-0.27)	**0.36** (0.23-0.54)
Type RT centre	Independent	ref.	ref.	ref.	ref.	ref.	ref.
	Hospital related	**1.43** (1.18-1.73)	1.14 (0.91-1.43)	**0.52** (0.35-0.77)	**0.44** (0.28-0.67)	**2.11** (1.66-2.67)	**1.71** (1.29-2.27)
	University	**3.65** (3.16-4.22)	**4.49** (3.78-5.33)	**2.85** (2.28-3.56)	**3.17** (2.46-4.07)	**4.28** (3.53-5.2)	**5.88** (4.64-7.46)
PBI treatment	no PBI	ref.	ref.	ref.	ref.	ref.	ref.

Continued on next page

Table 2: The odds ratios and 95% confidence interval of receiving ultra-hypofractionated schemes. Univariate and multivariate analyses over the periods 2020-2021, 2020 and 2021. (Continued)

	PBI	**14.17** (12.14-16.53)	**9.62** (8.03-11.52)	**9.98** (7.69-12.96)	**6.82** (5.0-9.31)	**15.87** (13.03-19.31)	**11.92** (9.47-15.0)
Periods	Pre-Covid	**0.12** (0.06-0.23)	**0.11** (0.06-0.21)	**0.12** (0.06-0.23)	**0.12** (0.06-0.23)	NA	NA
	Covid	**1.31** (1.05-1.62)	**1.35** (1.05-1.73)	**1.31** (1.05-1.62)	**1.37** (1.07-1.76)	NA	NA
	Post-Covid	ref.	ref.	ref.	ref.	ref.	ref.
	LPRM nov '20	**1.47** (1.2-1.8)	1.15 (0.9-1.46)	1.21 (0.94-1.56)	0.88 (0.65-1.19)	NA	NA
	LPRM apr '21	**1.97** (1.64-2.36)	**1.62** (1.31-2.01)	NA	NA	NA	NA

[a] *Travel time is the travel time by car from the patients' postal code to the RT institute.*

Statistically significant factors are indicated with bold values.
DCIS, Ductal Carcinoma in Situ; LPRM, National Platform Radiotherapy Breast Cancer; PBI, Partial Breast Irradiation; RT, Radiotherapy; SES, Socioeconomic status.

3.4 Questionnaire

In total 16 (84.21%) RT institutes responded out of 19 that received the questionnaire. The 5x5.2 Gy scheme was used for both partial breast irradiation (PBI) and whole breast irradiation (WBI) in all responding institutions. In addition to PBI and WBI, institutes also used 5x5.2 Gy for the thoracic wall, local (breast after BCS, thoracic wall after mastectomy) and axilla levels 1 and 2 (Figure 6).

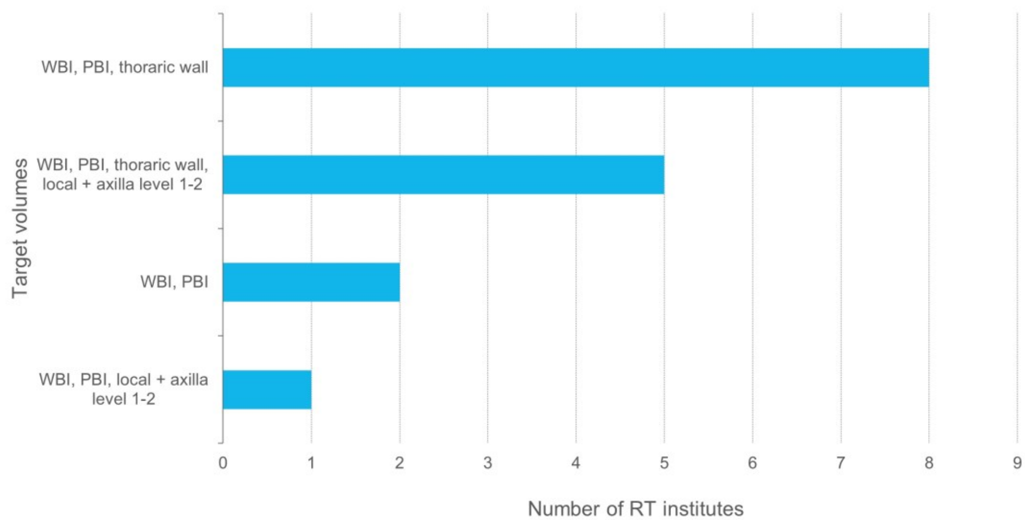

Figure 6: The number of RT institutes that implemented 5x5.2 Gy per target volumes. Local target volume is the breast after BCS and the thoracic wall after a mastectomy.

The decision on whether to implement 5x5.2 Gy was influenced by the use of a bolus (tissue-equivalent material). It was a reason for institutes not to implement the 5x5.2 Gy for WBI (n=2), PBI (n=2) and thoracic wall irradiation (n=6). For three institutes, the bolus did not affect the decision on whether to use 5x5.2 Gy. In addition, two institutes barely used or did not use a bolus in general. Three institutes used a bolus depending on the target volume (e.g. only for thoracic wall irradiation). One institute used the bolus only for palliative care and not for curative care. Furthermore, two institutes indicated that they did not know what a bolus was.

The institutes were asked whether they perceived a difference in the toxicity between five fractions and 15 fractions (or other longer schemes) in the acute or (middle) long period. This data was unknown for the majority of the institutes (n=9). Four institutes indicated there was no difference between these schemes. Three institutes responded that there was a difference. For one of the institutes, the toxicity seemed milder after five fractions. According to the second institute, less fatigue was perceived for five fractions and possibly less pain. And the last institute indicated that less toxicity was visible for the acute period.

3.4.1 Patient-related factors

In the majority of the institutes (n=15), age was one of the patient-related factors influencing the choice to implement 5x5.2 Gy with WBI, PBI, irradiation on the thoracic wall or (local and) axilla levels 1-2. In most institutes, the scheme was implemented for patients 50 years or older (Figure 7). One institute indicated that age was an influencing factor for all implemented target volumes, except for thoracic wall irradiation. This institute answered “other” for local and axilla levels 1 and 2 because the local irradiation after a mastectomy (irradiation on the thoracic wall) also did not have an age minimum and the local irradiation after a BCS (irradiation on the breast) was at least 40 years. Another institute replied “other” for WBI and thoracic wall irradiation. The institute implemented the schemes for patients who were 60 years and older for these two target volumes and for patients aged 50-60 years the decision was based on shared decision-making. For PBI there is an institute where the 5x5.2 Gy scheme was implemented for all ages. However, they implemented a specific type of partial breast irradiation called APBI (accelerated PBI that can include 5x6 Gy or 10 fraction schemes) for patients aged 50 and older. One institute responded that they did not implement ultra-hypofractionated schemes for PBI for patients younger than 40 years (i.e. they answered “other”).

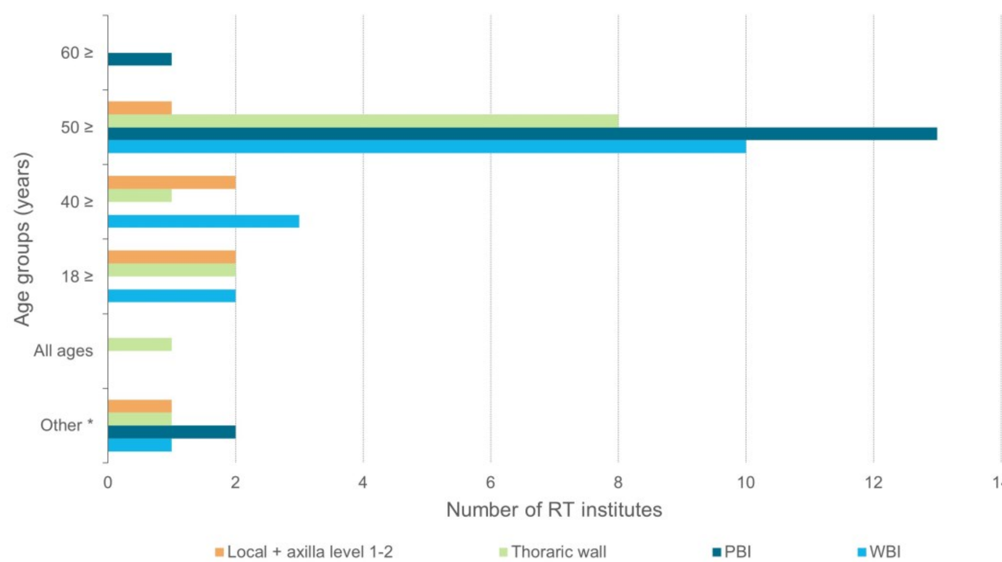

*Figure 7: The number of RT institutes that implemented 5x5.2 Gy per age group for the target volumes local and axilla levels 1 to 2, thoracic wall, PBI and WBI. * The other option is described in the text above.*

Other factors that influenced the decision whether to use 5x5.2 Gy were dosimetric inhomogeneity, wound (healing) problems, presence of (large) seroma, presence of (large) hematoma, complex/elaborate oncoplastic surgery, and post-operative oedema (Figure 8). Wound (healing) problems can be identified by infections, scarring or bleeding. In addition, for PBI, more than half of the institutes (n=9) did not consider factors not to implement 5x5.2 Gy. For WBI (n=2) and the thoracic wall irradiation (n=5), some institutes did not have influencing factors on the decision either. One institute indicated that smoking and complaints from patients were influencing factors in WBI, PBI and the thoracic wall.

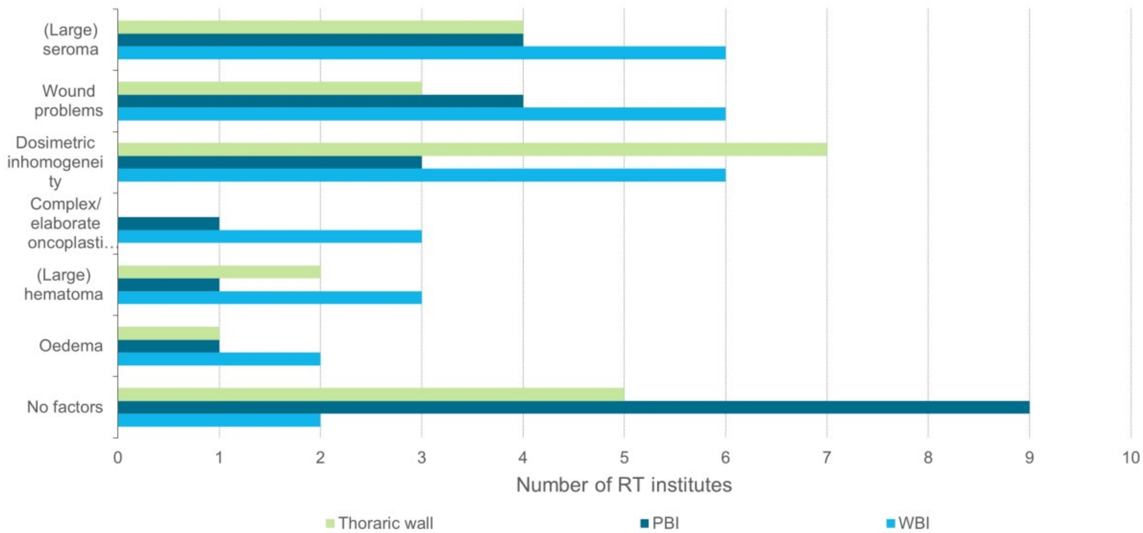

Figure 8: Reasons to not consider the 5x5.2 Gy scheme for patients for thoracic wall irradiation, PBI and WBI. Including the answers of the institutes that did not consider any factors not to implement 5x5.2 Gy.

Factors that only occurred once in WBI, PBI and thoracic wall irradiation are visible in Table 3. Furthermore, institutes were asked to indicate general reasons not to implement 5x5.2 Gy regardless of the target volume. General reasons were shared decision-making, the patient's wishes and postoperative infections with fibrosis. The answer to a follow-up question regarding the cup size for WBI in Table 3 indicated that the institute determined the implementation of the 5x5.2 Gy based on the patient. With larger cup sizes, longer schemes were used. This decision depended on the patient's age as well.

Table 3: Factors that influence the decision to implement the 5x5.2 Gy scheme. These factors were answered once or twice in the questionnaire.

	WBI	PBI	Thoraric wall
Prosthesis	x		x
T-DM1[a]	x		x
Chemotherapy right after RT	x		x
Cross-section	x		x
Volume		x	
Cupsize[b]	x		
Two operations	x		
Operation effect	x		
Protons			x
Direct reconstruction			x
Bolus			x

[a] *T-DM1 is an adjuvant HER2-target therapy.*

[b] *The follow-up question regarding the cup size indicated the institute determines the implementation of the 5x5.2 Gy depending on the patient. With larger cup sizes, longer schemes are used. This decision is also dependent on the age.*

3.4.2 Non-patient related factors

Several non-patient-related factors also influenced the decision on whether to implement the five fraction schemes. For two institutes the financing or reimbursement of the five fraction schemes led to a delayed implementation. However, the majority of the institutes (n=14) responded that it did not affect the decision. One institute mentioned that a technical reason for not implementing five fraction schemes was that some devices for the five fraction scheme could not be combined with breath-hold, therefore those devices are not compatible with the schemes.

According to the majority of the institutes, the COVID-19 pandemic influenced the decision to implement five fractions. The scheme was implemented mainly to reduce the pressure on the healthcare sector (n=9) and to prevent further infections of COVID-19 (n=9). Six institutes responded that the COVID-19 pandemic did not affect the decision. One institute responded that before the FAST and FAST-Forward trials were published, the toxicity of the new scheme was not known and therefore the implementation was delayed. Noticeable periods in 2020 and 2021 also had an impact on the implementation of the ultra-hypofractionated schemes for the first time. The start of the COVID pandemic (spring 2020) and the LPRM meetings in November 2020 and April 2021 significantly increased the implementation of the five fraction schemes (Figure 9). One institute indicated that they implemented the five fraction scheme on a large scale after the LPRM meetings for WBI, PBI and thoracic wall irradiation. For one institute the five fraction schemes were implemented in 2023 for WBI and PBI and in 2024 for thoracic wall irradiation.

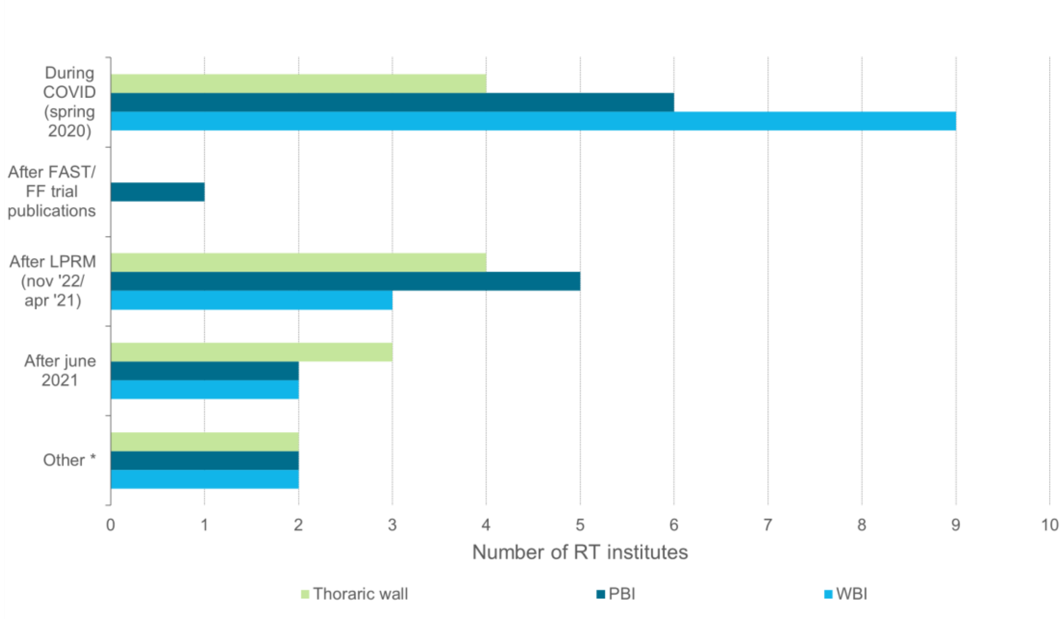

*Figure 9: Noticeable moments (Figure 1) during the study period after which the 5x5.2 Gy and/or 5x5.7 Gy schemes were first implemented. *The answers of the institutes who answered "other" were described in the text above.*

4 Discussion

The use of ultra-hypofractionated schemes has increased for non-metastatic, surgically treated breast cancer patients during the study period (2020-2021). In 2021, the schemes were implemented to a larger extent than in 2020. In addition, there was more variation between the RT institutes in 2021. According to the data analysis and questionnaire, the start of the COVID-19 pandemic in the Netherlands, the schemes peaked in use, especially the 5x5.2 Gy and the 5x5.7 Gy schemes. These peaks were due to the institutions' desire to reduce the pressure on healthcare and to prevent infections. From June 2020, the 5x5.2 Gy scheme increased in use and from March 2021 the 5x5.7 Gy scheme decreased. The patient's age, tumour size, lymph node involvement, type of RT centre, PBI treatment and the period of administration were significant factors for implementing the ultra-hypofractionated schemes (5x5.2 Gy, 5x5.7 Gy, 5x6 Gy) according to logistic regression. The RT institutes indicated in the questionnaire that (large) seromas, wound problems and dosimetric inhomogeneity were frequently answered factors not to implement the schemes. In addition, age influenced the decision on the implementation of ultra-hypofractionated schemes.

During the start of the COVID-19 period, the implementation of the ultra-hypofractionated schemes significantly increased which was visible in both the data analysis and questionnaire. This change was also visible for other countries (e.g. U.S. [23] and the U.K. [24]). The increase in the use of the 5x5.2 Gy and 5x5.7 Gy schemes could be due to the follow-up publications of the FAST-Forward and FAST trials. These publications showed the non-inferior results of using these schemes compared to more conventional methods [14,15]. Another stimulating factor could be the publication of the international guidelines which also mentioned the FAST and FAST-Forward trials [18]. The LPRM meetings in November 2020 and April 2021 were also popular events after which to implement the schemes for the first time, visible in both data analysis and the questionnaire. The higher peak of the 5x5.7 Gy scheme compared to the 5x5.2 Gy can be explained by the one weekly implementation. This made it for example easier to change the irradiation day during the week. The longer follow-up period of the FAST trial compared to that of the FAST-Forward might also have influenced the peak. However, the larger population and the primary outcome of the FAST-Forward trial together with the shorter treatment period of one week, caused the 5x5.2 Gy scheme to further increase in use in 2020 regardless of the shorter follow-up period compared to the 5x5.7 Gy scheme, which decreased.

The 5x6 Gy scheme was mostly used for PBI and also increased in use in 2020. The follow-up publications from August 2020 of the Florence trial could explain this increase and PBI use. The trial compared the 5x6 Gy scheme in APBI with the conventional 25x2 Gy scheme for WBI for women older than 40 and with early breast cancer. The difference in IBTR rates was not significant between the two RT schemes. Acute and late toxicity and cosmetic outcomes were significantly better for APBI than WBI [16,25].

In the questionnaire, two institutes indicated that there was a financial influence on the decision to implement the 5x5.2 Gy scheme. From the beginning of 2020, there was only reimbursement for RT schemes six fractions or higher. This could explain the delayed implementation for the two institutes. Other institutes did not mention any financial influence or they might not have known about the reimbursement.

Three institutes also indicated in the questionnaire a change in acute toxicity or toxicity over a (middle) long period comparing the five fraction and 15 fraction schemes. The differences were in favour of the five fraction scheme. Four institutes indicated they did not perceive a difference between the two irradiation schemes. This is in line with a sub-study of the FAST-Forward trial in 2016 which showed an unlikeliness of more severe acute skin toxicity between the five fraction and the 15 fraction schedule [26]. In further research, this might be monitored for further insight into the toxicity of the ultra-hypofractionated schemes.

According to the logistic regression, there were higher odds of the implementation of the five fraction schemes with higher age, no lymph node involvement, smaller tumour size, university-related RT centre, first implementation period and use of PBI. The FAST trial [15] and the study of K.L. Corrigan et. al. [27] confirmed that patients with a lower risk of local recurrence had a higher chance of receiving ultra-hypofractionated schemes. These patients can be identified by higher age, lower tumour grade and no lymph node involvement. Furthermore, PBI is considered a standard procedure in lower-risk patients in the Netherlands (i.e. patients 50 years and older, smaller tumours, ER positive and HER2 negative). This age minimum is also explained by the questionnaire where PBI is only implemented with 5x5.2 Gy for patients 50 years and older following the ASTRO guidelines from 2017 [28]. Furthermore, Dutch clinicians indicated that the ASTRO guidelines [29] are followed in general. These findings further confirm the higher odds of receiving five fractions for lower-risk patients in combination with the higher odds of receiving five fractions for patients who receive PBI. In further research, the target volumes considered in the questionnaire could also be considered during the data analysis because of the significance of PBI according to the logistic regression and the difference in influencing factors according to the questionnaire. For further research, a difference between WBI, PBI and thoracic wall irradiation might be considered in data analysis.

There were several limitations in this study. First, there was a difference in the study period between the data analysis and the questionnaire. The study period of the data of the NCR and NBCA-R was 2020 to 2021. The questionnaire sent to the Dutch RT institutes included questions about the implementation of the five fraction schemes and included answers for April and May 2024. There might be a change in influencing factors after 2021 that can be explained by the results of the questionnaire. To investigate possible changes in the implementation of the five fraction scheme, further data research could be done for the years after 2021. Secondly, there could be a difference in analysed RT institutes (n=12) in the data and the responding institutes of the questionnaire (n=16). This might lead to not knowing the reasons from institutes that did not implement 5x5.2 Gy. The questionnaire was anonymous and therefore it was not possible to check whether the RT institutes from the data overlap those of the questionnaire. Thirdly, synchronous tumours were included. These are tumours diagnosed one or three months apart from another, often resulting in a combined treatment path. This led to the inclusion of the same treatment path for the same patient with multiple diagnosed tumours, increasing double-included treatments. Lastly, two institutes indicated that they did not know what a bolus was in the questionnaire. They might know a different definition of this technique and still consider it an influencing factor on the decision on whether to use five fractions.

5 Conclusion

The implementation of the ultra-hypofractionated RT schemes was higher in 2021 compared to 2020. In addition, more variation between the institutes was visible in 2021. The implementation of ultra-hypofractionated schemes, especially 5x5.2 Gy and 5x5.7 Gy, increased from the start of the COVID-19 pandemic followed by the further increase of the 5x5.2 Gy scheme throughout 2021. According to the questionnaire, reasons for implementing the ultra-hypofractionated schemes during the COVID-19 pandemic were to reduce the chance of infections and reduce pressure on healthcare. Other important factors after which the implementation of the schemes increased were the LPRM meetings. Low-risk patients (higher age, no lymph node involvement, smaller tumour size), university-related RT centres and PBI treatment were also important factors for the implementation of the five fraction schemes. Dosimetric homogeneity, wound (healing) problems and (large) seromas were according to the institutes important factors that influenced the decision to no implement the five fraction schemes. Future studies should monitor the development of the implementation of the ultra-hypofractionated schemes.

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A Appendix questionnaire

Remarks about the questionnaire:

The following questions were translated from the Dutch version of the questionnaire that was distributed.
⊗This sign is visible in multiple choice questions. When this answer option is selected, all other multiple choice answer options in that question are deselected.
Square answer options mean it is a multiple choice question, round answer options are single choice questions.

Ultra-hypofractionation questions

General introduction: This is an anonymous questionnaire about ultra-hypofractionated radiotherapy schemes among breast cancer patients. The questionnaire focusses on the 5x5.2 Gy arm from the FAST-Forward trials.

Please answer 1 questionnaire per institute.
Expected time is 10-15 minutes.

Q1
Which of the following target volumes do you use the 5x5.2 Gy scheme for? (Multiple answers possible)

- ☐ Whole Breast Irradiation (WBI)
- ☐ Partial Breast Irradiation (PBI)
- ☐ Thoraric wall irradiation
- ☐ Local + axilla levels 1-2
- ☐ Local + axilla levels 1/2 to 4
- ☐ Local + axilla level 1/2 to 4 and parasternal
- ☐ Axilla levels 1-2
- ☐ Axilla level 1/2 to 4
- ⊗ None of the above, namely ____

The following questions focus on factors of influence on the decision to irradiate or not with 5x5.2 Gy.

Q2

Show question if:
Q1 is answered with: Whole Breast irradiation (WBI)

What factors contribute to the decision to irradiate using the 5x5.2 Gy scheme with **WBI**? (multiple answers possible)

- ☐ Cupsize, namely... (see follow-up question on next page)
- ☐ Volume
- ☐ Cross-section
- ☐ Inhomogeneity
- ☐ Other, namely ______
- ⊗ None of these factors influence the decision

Q3

Show question if:	
Q2 is answered with:	Cupsize, namely... (see follow-up question on next page)

What cupsizes contribute to the decision to irradiate with the 5x5.2 Gy scheme with WBI? (follow-up question)

- ☐ From cupsize D
- ☐ From cupsize E
- ☐ From cupsize F
- ☐ From cupsize G
- ☐ Other, namely ________

Q4

Show question if:	
Q1 is answered with:	Whole Breast Irradiation(WBI)

In case of **WBI**, does the use of 5x5.2 Gy depend on age?

- ○ Yes, from the age of 40
- ○ Yes, from the age of 50
- ○ Yes, from the age of 60
- ○ Yes, from the age of 70
- ○ No
- ○ Other, namely ________

Q5

Show question if: Q1 is answered with: Local + axilla levels 1-2 Or Local + axilla levels 1/2 to 4

In case of **local + axilla levels 1/2 (to 4)** as target volume, does the use of 5x5.2 Gy depend on age?

- ◯ Yes, from the age of 40
- ◯ Yes, from the age of 50
- ◯ Yes, from the age of 60
- ◯ Yes, from the age of 70
- ◯ No
- ◯ Other, namely ______

Q6

Show question if: Q1 is answered with: Thoraric wall irradiation

What factors contribute to the decision to irradiate using the 5x5.2 Gy scheme with **thoraric wall irradiation**? (multiple answers possible)

- ☐ Cross-section
- ☐ Inhomogeneity
- ☐ Other, namely ______
- ⊗ None of these factors influence the decision

Q7

Show question if:
Q1 is answered with: Thoraric wall irradiation

In case of thoraric wall irradiation, does the use of 5x5.2 Gy depend on age?

- ◯ Yes, from the age of 18
- ◯ Yes, from the age of 30
- ◯ Yes, from the age of 40
- ◯ Yes, from the age of 50
- ◯ Yes, from the age of 60
- ◯ Yes, from the age of 70
- ◯ No
- ◯ Other, namely ____________

Q8

Show question if: Q1 is answered with: Partial Breast Irradiation (PBI)

What factors contribute to the decision to irradiate using the 5x5.2 Gy scheme with **PBI**? (multiple answers possible)

- ☐ Cupsize, namely... (see follow-up question on next page)
- ☐ Volume
- ☐ Cross-section
- ☐ Inhomogeneity
- ☐ Other, namely ______
- ⊗ None of these factors influence the decision

Q9

Show question if: Q8 is answered with: Cupzise, namely... (see follow-up question on next page)

What cupsizes contribute to the decision to irradiate with the 5x5.2 Gy scheme with **PBI**? (follow-up question)

- ☐ From cupsize D
- ☐ From cupsize E
- ☐ From cupsize F
- ☐ From cupsize G
- ☐ Other, namely ______

Q10

Show question if:
Q1 is answered with: Partiële borstbestraling (PBI)

In case of **PBI**, does the use of 5x5.2 Gy depend on age?

- ◯ Yes, from the age of 40
- ◯ Yes, from the age of 50
- ◯ Yes, from the age of 60
- ◯ Yes, from the age of 70
- ◯ No
- ◯ Other, namely ____

Q11
Is the use of a bolus a reason not to implement 5x5.2 Gy? (multiple answers possible)

- ☐ Yes, with WBI
- ☐ Yes, with PBI
- ☐ Yes, with thoraric wall irradiation
- ☐ No
- ☐ Other, namely ____

Q12
Are there other **patient related** reasons not to implement 5x5.2 Gy?

____

Q13
Do you see a difference in the collected toxicity data until now of acute and (middle) long period toxicity between five fractions and 15 fractions (/ longer schemes)

- ◯ Unkown
- ◯ No
- ◯ Yes, namely … [ ]

Q14
Does the reimbursement of the ultra-hypofractionated scheme influence the implementation of the scheme?

- ◯ Yes, because of this it was not implemented
- ◯ Yes, this delayed the implementation
- ◯ There was limited implementation (e.g. only PBI), namely [ ]
- ◯ No

Q15
Are there other non-**patient related** reasons to implement 5x5.2 Gy?

[ ]

Q16

Show question if:
Q1 is answered with: Whole Breast Irradiation (WBI)

What was the first time you implemented the ultra-hypofractionated scheme in case of **WBI**?

- ◯ During the COVID pandemic (spring 2020)
- ◯ After the publications of the FAST-Forward and FAST trials (summer 2020)
- ◯ After the LPRM meetings (November 2020/ April 2021)
- ◯ Not implemented
- ◯ Unkown
- ◯ Other, namely ...

Q17

Show question if:
Q1 is answered with: Partial Breast Irradiation (PBI)

What was the first time you implemented the ultra-hypofractionated scheme in case of **PBI**?

- ◯ During the COVID pandemic (spring 2020)
- ◯ After the publications of the FAST-Forward and FAST trials (summer 2020)
- ◯ After the LPRM meetings (November 2020/ April 2021)
- ◯ Not implemented
- ◯ Unkown
- ◯ Other, namely ...

Q18

Show question if:
Q1 is answered with: Thoraric wall irradiation

What was the first time you implemented the ultra-hypofractionated scheme in case of **thoraric wall irradiation**?

- ◯ During the COVID pandemic (spring 2020)
- ◯ After the publications of the FAST-Forward and FAST trials (summer 2020)
- ◯ After the LPRM meetings (November 2020/ April 2021)
- ◯ Not implemented
- ◯ Unkown
- ◯ Other, namely ...

Q19

Did the COVID-19 pandemic contributed to the implementation of the ultra-hypofractionated scheme? If so, in what way? (multiple answers are possible)

- ☐ Yes, it was implemented to reduce the pressure on the healthcare sector
- ☐ Yes, it was implemented to reduce the chance of COVID-19 infections
- ☐ Yes, the implementation of the scheme was delayed because of the unknown toxicity in the start (before the publications of the follow ups of the FAST and FAST-Forward trials)
- ☐ Yes, the implementation of the scheme was delayed because of the pressure on the healthcare sector
- ⊗ No, the COVID-19 pandemic did not contribute to the implementation.
- ☐ Other, namely ...

B Appendix accronyms

APBI	Accelerated Partial Breast Irradiation
BCS	Breast Conserving Surgery
CI	Confidence interval
DCIS	Ductal Carcinoma in Situ
ES	Estrogen
Gy	Grey
HER2	Human Epidermal Growth Factor receptor 2
IBTR	Ipsilateral Breast Tumour Recurrence
IKNL	Netherlands Comprehensive Cancer Registry
LPRM	National Platform Radiotherapy Breast Cancer
NBCA-R	NABON Breast Cancer Audit Radiotherapy
NCR	Netherlands Cancer Registry
NVRO	Netherlands association for Radiotherapy and Oncology
PBI	Partial Breast Irradiation
PR	Progesterone
PST	Primary systematic therapy
RT	Radiotherapy
SES	Socioeconomic status
TNM	Tumour, Node, Metastasis
WBI	Whole breast irradiation