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Editorial

Accelerated Adaptation of Ultrahypofractionated Radiation Therapy for Breast Cancer at the Time of the COVID-19 Pandemic

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Early in March 2020, the SARS-CoV-2 (COVID-19) pandemic struck Belgium [1]. Our large radiation oncology department took immediate precautionary measures to prevent COVID-19-induced saturation of health resources that may lead to delays and possibly the inability to provide radiation therapy to our patients. As part of the emergency adjustments, we implemented an ultrahypofractionation scheme of 26 Gy in five consecutive fractions, based on the FAST-Forward trial, for postoperative radiation therapy of breast cancer patients [2,3]. Prior to the COVID-19 pandemic, our protocol was 40 Gy in 15 daily fractions for 3 consecutive weeks. As 30% of our patients are breast cancer patients, we anticipated that adopting ultrahypofractionation in this population would have the largest impact on reducing infection risks for patients and staff.

Here we describe the measures taken to introduce and apply this protocol, treatment delivery experiences and early toxicity of treated patients.

Methods

Ultrahypofractionation was offered to all eligible patients and was therefore not regarded as a prospective trial. Informed consent was achieved for radiation therapy. Data were recorded in a prospective database. The reporting of outcomes was approved by the institutional ethics committee (CTOR20067GZA).

Prior to the introduction of the protocol, the following measures were taken by the radiation therapy team:

- The protocol was discussed and accepted within the multidisciplinary breast cancer team.
- Radiation therapy planning and delivery procedures were reviewed by the radiation therapy team [3]. Our routine computed tomography-based isocentric intensity-modulated radiation therapy sliding window treatment technique (i.e. irregular surface correction) was used, based on clinical target volumes according to the European Society for Radiotherapy and Oncology (ESTRO) guidelines [4]. If indicated ($n = 4$), axillary lymph node levels 1 and 2 up until the caudal border of axillary vessels were included. Respiratory control was considered in all left-sided breast cancer patients. A single boost dose of 6 Gy was delivered using an intensity-modulated radiation therapy technique for deeply seated tumours and a single electron field for superficial tumours [cut-off: Euclidian skin-to-caudal planning target volume distance <3 cm, i.e. maximum 9 MeV]. The dose prescription was according to ICRU 50 [5]. Plans were evaluated according to the FAST-Forward trial planning objectives. Daily kV/kV-based position and transit electronic portal image device (EPID) dosimetric verification was carried out.
- After reviewing and discussing the protocol with the FAST-Forward trial team (the full paper was still pending publication), we identified the need for a tumour bed boost as the FAST-Forward trial population was relatively low risk. While the FAST-Forward trial allowed for a sequential fractionated boost, we

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preferred to avoid further treatment prolongation during COVID-19 times. Using the linear-quadratic model with an α/β value of 3, we estimated 6 Gy in one fraction to the tumour bed being equivalent to 10 Gy in five fractions.

- The protocol adopted by our department was planned for all node-negative patients referred for post-operative whole breast radiation therapy or patients $\geq$70 years with low-risk node-positive disease. A sequential boost was delivered to all patients <70 years.
- As elective patient contacts were discouraged during the pandemic, we carried out tele-medicine follow-up [6].
- Despite available evidence, concerns existed that ultrahypofractionation would lead to more severe or longer-lasting early skin reactions compared with 40 Gy in 15 fractions, especially including a hypofractionated boost. Therefore, we decided to carry out a tele-medicine follow-up weekly after completing radiation therapy. Data on side-effects were recorded using the Common Terminology Criteria for Adverse Events (CTCAE) v.5 and the European Organization for Research and Treatment of Cancer (EORTC)-Breast (QLQ-BR23) questionnaires (see Table 1). A descriptive statistical analysis of toxicity was carried out; the significance of differences was assessed using the Pearson chi-squared test and *P*-values < 0.05 were taken to indicate statistical significance.

Results

Between 24 March and 2 June 2020,102 breast cancer patients were treated with ultrahypofractionation. Treatment preparation and delivery went as planned. Of the 544 delivered fractions, only 20 fractions (3.7%) did not pass the transit dosimetry tolerance level of 98%, mostly related to respiration and/or swelling of the breast.

Clinical and Treatment Outcomes

All 102 patients successfully completed radiation therapy. Sixty-eight patients had already had at least one tele-medicine follow-up and were included for toxicity analysis. The median follow-up was 32 days (range 8–54). Patient-, tumour- and treatment-related characteristics are listed in Table 2. The prevalence of the most-reported grade 1 early breast toxicity after treatment was 74% for dermatitis, 68% for fatigue and 38% for oedema (Table 3). Grade 2

Table 1
Outline of the tele-medicine questionnaire, based on the Common Terminology Criteria for Adverse Events (CTCAE) v.5 (upper part) and European Organization for Research and Treatment of Cancer (EORTC) QLQ-BR23 (lower part) questionnaires

0		1	2	3
Radiation dermatitis	None	Faint erythema Dry desquamation	Moderate to brisk erythema, mostly in skin folds Moderate oedema	Confluent moist desquamation, other than skin folds Bleeding induced by minor trauma
Breast oedema		Asymptomatic	Symptomatic (pain or psychosocial impact)	Severe symptoms Intervention needed Enlarge radiation therapy fields
Pain of skin		Mild	Moderate pain Limiting instrumental ADL	Severe pain Limiting self-care ADL
Fatigue		Relieved by rest	Fatigue not relieved by rest Limiting instrumental ADL	Fatigue not relieved by rest Limiting self-care ADL
	0	1	2	3
Did you have any pain in your arm or shoulder? Did you have a swollen arm or hand? Was it difficult to raise your arm or to move it sideways? Have you had any breast pain? Have you had any increased breast sensitivity? Have you had skin problems on the breast (e.g. itchy, dry, flaky)?	Not at all	A little bit	Quite a bit	Very much

ADL, activities of daily living.

Table 2
Patient-, tumour- and treatment-related characteristics

	Patients (*n*)	%		Patients (*n*)	%
Age (years)			Hormone receptor status		
≤40	0	0	ER		
41–50	7	10	Unknown	1	1
51–60	8	12	Positive (Allred >2)	60	88
>60	53	78	Negative	7	10
WHO status			PR		
Unknown	18	26	Unknown	1	1
0	34	50	Positive (Allred >2)	50	74
1	14	21	Negative	17	25
≥2	2	3			
Tumour size (mm)					
Unknown	5	7	Her2		
<5	9	13	Unknown	3	4
6–10	18	27	0	10	15
11–20	26	38	1+	31	46
21–50	10	15	2+	18	26
>50	0	0	3+	6	9
			Nodal assessment		
Histological type					
IDC	47	69	Unknown	1	1
ILC	11	16	Sentinel node biopsy	62	91
IDC/ILC	1	1	Axillary node dissection	1	1
DCIS	4	6	None (DCIS)	4	6
Other	5	7			
			Number of positive nodes		
Histological grade			Unknown	2	3
Unknown	1	1	0	59	87
1	22	32	1–3	7	10
2	31	46	4+	0	0
3	14	21			
			Radiation treatment		
Presence of LVI			Tumour bed boost	43	63
Unknown	2	3	Regional lymph node irradiation	4	6
Yes	0	0			
No	66	97	Adjuvant therapy		
			Endocrine therapy	62	91
Presence of PNI			Chemotherapy	3	4
Unknown	2	3	No adjuvant therapy	3	4
Yes	1	1			
No	65	96			
Tumour focality					
Unifocal	64	94			
Multifocal	4	6			

DCIS, ductal carcinoma *in situ*; ER, oestrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PNI, perineural Invasion; PR, progesterone receptor.

toxicity was reported by 7% for fatigue and 3% for dermatitis. No grade ≥3 toxicity was seen. Most toxicity was seen 3 weeks after the completion of radiation therapy (Figure 1). The prevalence of CTCAE toxicity is demonstrated in Figure 2, showing no significant differences between patients receiving a boost and patients not receiving a boost.

Discussion

Here we report the accelerated implementation of ultrahypofractionation for postoperative breast radiation therapy at the time of a major worldwide health crisis. Early in the COVID-19 pandemic in Belgium, we found that rapid adjustments were needed to ensure continuity of care for patients without compromising oncological outcome and to reduce the potential infectious risks for patients and staff. As our centre treats about 1000 breast cancer patients a year, we decided to adopt ultrahypofractionation for postoperative radiation therapy for breast cancer to significantly reduce potential exposure of patients and staff, while providing treatment without delay. The low rates of early toxicity, as previously shown in the FAST-Forward trial, encouraged us to make this choice, while efficacy results were then still pending publication [3,6].

Table 3
Incidence of highest reported radiation toxicity and breast irradiation side-effects

	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]
Dermatitis	50 (74)	2 (3)	0 (0)
Oedema	26 (38)	1 (1)	0 (0)
Pain	24 (35)	0 (0)	0 (0)
Fatigue	46 (68)	5 (7)	0 (0)
	Not at all [*n* (%)]	A little bit [*n* (%)]	Quite a bit [*n* (%)]
Pain in arm/shoulder	64 (94)	4 (6)	0 (0)
Swollen arm/hand	65 (95)	3 (4)	0 (0)
Difficult arm movement	64 (94)	4 (6)	0 (0)
Breast pain	26 (38)	36 (53)	6 (9)
Increased breast sensitivity	28 (41)	36 (53)	4 (6)
Skin problems (e.g. itchy, dry, flaky)	19 (28)	42 (62)	5 (7)

We aimed to select comparable patients with those eligible for the FAST-Forward trial; nonetheless, when resources at our department decreased further due to staffing problems, we also included selected node-positive patients, avoiding irradiation of the brachial plexus by limiting the nodal target volume up until the caudal part of the axillary vessels.

Importantly, the implementation of a radiobiological equivalent hypofractionated tumour bed boost was unique. Similar to other studies about hypofractionation of whole-breast radiation therapy, hypofractionation of the tumour bed boost was lacking behind in the FAST-Forward trial protocol. We did not expect increased early toxicity rates as the biological equivalent dose remained the same as with conventional fractionation. This was confirmed by the unchanged early toxicity rates of patients treated with a boost versus those treated without a boost in our cohort (Figure 2). Regarding late toxicity, this hypofractionated boost might hypothetically impact cosmetic outcome adversely as the EqD2 dose is 2 Gy higher when assuming

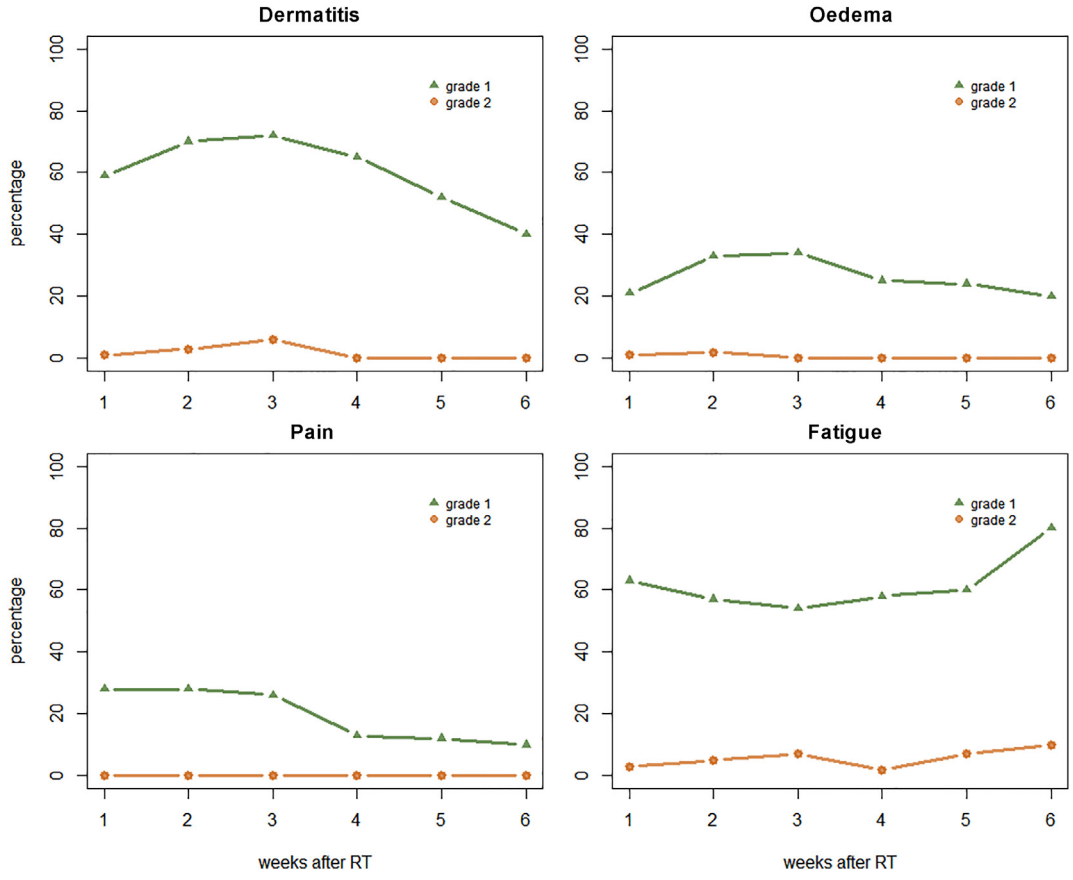

Fig 1. Prevalence of grade 1 and grade 2 Common Terminology Criteria for Adverse Events (CTCAE) toxicity (v.5).

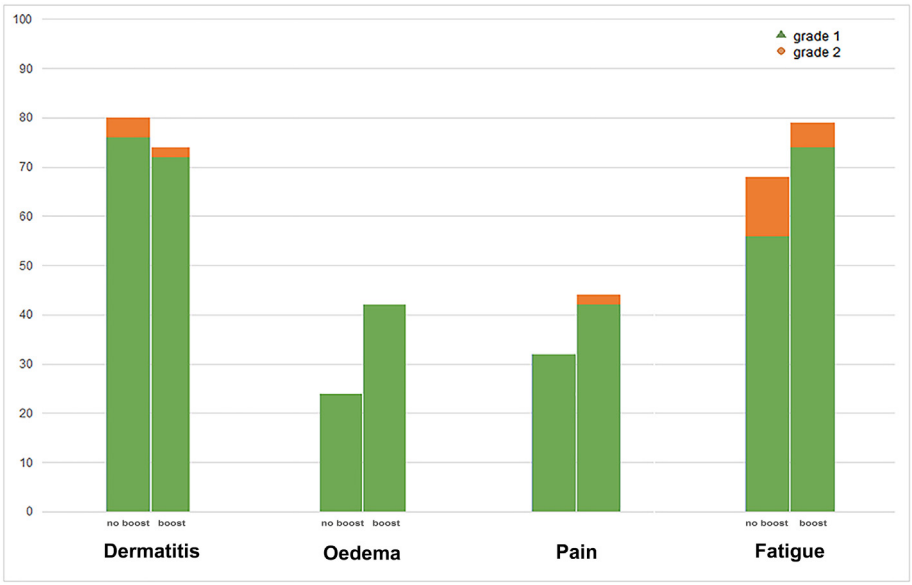

Fig 2. Prevalence of highest reported Common Terminology Criteria for Adverse Events (CTCAE) toxicity for patients receiving a tumour bed boost versus no tumour bed boost (right and left column, respectively). No significant differences were found between groups.

an α/β value of 2 for late effects. Before routine implementation post-COVID-19, this should be further investigated.

We aimed to keep the workload for staff as low as reasonably achievable. Therefore, most of the treatment preparation of ultrahypofractionation was identical to our former radiation therapy breast protocol of 40 Gy in 15 fractions. No difficulties were noted during treatment preparation. Two adaptations made were the implementation of a daily kV/kV set-up verification instead of an eNAL procedure, and daily transit EPID dosimetry with integrated images, for quality assurance [7]. Of the delivered fractions, only 20 (3.7%) did not pass the tolerance level of 98%. This is lower than the observed 8% not passing the tolerance level in a historical cohort of node-negative patients treated at our department pre-COVID with the 40/15 scheme. Probable explanations are the reduced overall treatment time and daily kV/kV set-up verification.

After completing radiation therapy, low rates of clinically significant early toxicity were seen, similar to the FAST-Forward trial [6]. A peculiar finding is the lack of grade 3 toxicity, possibly partially explained by the use of tele-medicine, which might induce – despite thoroughly questioning the patient – an underestimation of toxicity. The use of tele-medicine is also the most important limitation of our report, but because our primary goal was to reduce patient exposure to COVID-19 in crowded hospitals, this was inevitable. Nevertheless, studies have shown that these tele-medicine follow-ups can be equally effective as routine hospital visits [8,9].

In conclusion, ultrahypofractionation was fluidly implemented in our departmental workflow. We also noted no negative influence on general staff and patient satisfaction. It allowed a reduction in potential exposure of patients and staff to COVID-19 and enabled treatment delivery without delay. Furthermore, improved treatment accuracy and low early toxicity rates were shown. These findings endorse our continued use of ultrahypofractionation for all node-negative patients after the COVID-19 pandemic, while for the ultrahypofractionated boost we will contribute to initiating prospective research.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author (MM). The data are not publicly available due to institutional ethics policy, as they contain information that could compromise the privacy of research participants.

Conflicts of Interest

The authors declare no conflict of interest.

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