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Original Research Article

Comparing treatment uncertainty for ultra- vs. standard-hypofractionated breast radiation therapy based on in-vivo dosimetry

Yawo A.C. Fiagan [a,b,*], Evy Bossuyt [a], Melanie Machiels [a,c], Daan Nevens [a,c], Charlotte Billiet [a,c], Philip Poortmans [a,c], Thierry Gevaert [b,d], Dirk Verellen [a,c]

[a] Iridium Netwerk, Radiation Oncology, Antwerp, Belgium
[b] Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium
[c] Faculty of Medicine and Health Sciences, Center for Oncological Research (CORE), Integrated Personalized and Precision Oncology Network (IPPON), Universiteit Antwerpen, Antwerp, Belgium
[d] Department of Radiation Oncology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

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ABSTRACT

Background and purpose: Postoperative ultrahypofractionated radiation therapy (UHFRT) in 5 fractions (fx) for breast cancer patients is as effective and safe as conventionally hypofractionated RT (HFRT) in 15 fx, liberating time for higher-level daily online Image-Guided Radiation Therapy (IGRT) corrections. In this retrospective study, treatment uncertainties occurring in patients treated with 5fx (5fx-group) were evaluated using electronic portal imaging device (EPID)-based in-vivo dosimetry (EIVD) and compared with the results from patients treated with conventionally HFRT (15fx-group) to validate the new technique and to evaluate if the shorter treatment schedule could have a positive effect on the treatment uncertainties.
Materials and methods: EPID-based integrated transit dose images were acquired for each treatment fraction in the 5fx-group (203 patients) and on the first 3 days of treatment and weekly thereafter in the 15fx-group (203 patients). A total of 1015 EIVD measurements in the 5fx-group and 1144 in the 15fx-group were acquired. Of the latter group, 755 had been treated with online IGRT correction (i.e., Online-IGRT 15fx-group).
Results: In the 15fx-group 12.0% of fractions failed (FFs) compared to 3.8% in the 5fx-group and 6.9% in the online-IGRT 15fx-group. Causes for FFs in the 15fx-group compared with the 5fx-group were patient positioning (7.4% vs. 2.2%), technical issues (3.1% vs. 1.2%) and breast swelling (1.4% vs. 0.5%). In the online-IGRT 15fx-group, 2.5% were attributed to patient positioning, 3.8% to technical issues and 0.5% to breast swelling.
Conclusions: EIVD demonstrated that UHFRT for breast cancer results in less FFs compared to standard HFRT. A large proportion of this decrease could be explained by using daily online IGRT.

1. Introduction

Quality assurance (QA) programs are designed to improve the quality and the safety of radiation treatments, including machine- and patient-specific QA [1,2]. The latter can be performed prior to treatment (pre-treatment verification) or during beam delivery (in-vivo dosimetry, IVD) [3,4]. IVD is recommended by many national and international organizations as a dosimetric safety tool to avoid major errors and to enhance accuracy [5–8]. Various IVD approaches are available including the traditional point detector measurement approach of which the use is limited for Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) due to many dose gradients and angles of incidence [9]. Currently, IVD methods increasingly introduced into clinical routine are electronic portal imaging device (EPID) approaches. EPIDs are present on modern linear accelerators, offering the possibility to perform patient position and dosimetric verification in 2D/3D, and automation [9,10]. Several studies have shown the sensitivity and effectiveness of EPID-based IVD (EIVD) for different treatment sites and relevant deviations encountered in clinical routine [11–14].

Recently, publications have reported the clinical use of a commercially available automated system for EIVD for patient-specific QA and IVD [15,16]. Bossuyt *et al.*, published the first report of the clinical use of this system for pre-treatment and EIVD, showing the system's capability

* Corresponding author at: GZA Hospitals, Sint-Augustinus-Iridium Netwerk, Oosterveldlaan 24, 2610 Wilrijk, Antwerp, Belgium.
E-mail address: Yawo.Fiagan@gza.be (Y.A.C. Fiagan).

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to detect various types of errors and deviations using empirically determined parameters [16]. Olch *et al.* demonstrated the automated EIVD's potential to identify changes in patient anatomy, patient setup, beam delivery and imager position [17,18].

In the treatment chain errors and uncertainties can occur that affect the accuracy of the delivered dose to the patient. Experience shows that setup and organ motion uncertainties are a major source of deviations during EIVD verification procedures routinely practiced [19–21]. These uncertainties can mainly be attributed to the use of the immobilization devices, correction strategies, patient body habitus and expertise of RTTs. To address the challenge of reproducing patient setup on a daily basis and reducing geometrical uncertainties image-guided radiotherapy (IGRT) protocols have been introduced. With the new on-board imaging technologies, IGRT protocols can be broadly divided into offline and online categories [22,23]. For the latter, daily pre-treatment position verification and immediate correction of the setup deviation is applied to improve patient positioning [24]. Leonard *et al.* reported that a daily IGRT protocol can be successfully used in an accelerated hypofractionated breast IMRT protocol for daily treatment accuracy [25]. On the other hand, offline IGRT protocols including no-action-level (NAL) and extended no-action-level (e-NAL) protocols require fewer images for a predefined number of fractions, and then, a correction is performed on subsequent fractions [26].

Additional uncertainties occurring due to motion from breathing or coughing cause the deviation of delivered dose that can be observed in dose-volume histograms (DVHs) [27]. Cerviño *et al.* reported that deep inspiration breath hold (DIBH) techniques can significantly mitigate some of these uncertainties reducing tumour bed motion and increasing heart and lung sparing [28]. It has been also reported that interfractional positional errors are large with DIBH technique and errors associated with these uncertainties can be minimized using a daily IGRT protocol [29]. Following the publication of long-term results of the FAST Forward trial [30,31], we implemented postoperative ultrahypofractionated RT (UHFRT) after breast conserving surgery (BCS). In the current study, we compared treatment uncertainties encountered in clinical routine in two cohorts of patients treated with UHFRT and standard hypofractionated RT (HFRT) schedules using an automated system for 2D EIVD. Secondly, the influence of IGRT protocols was investigated. Lastly, the effects of using breath hold techniques on treatment accuracy was investigated.

2. Materials and methods

2.1. Patient selection and ethics statement

From March to September 2020, a test group of 203 patients with breast cancer was treated with UHFRT of 26 Gy in 5 consecutive fractions (fx) during 1 week after BCS (i.e., 5fx-group); and one year before, a control group of 203 patients with breast cancer were treated with conventionally HFRT of 40 Gy in 15 consecutive fx, during 3 weeks following BCS (i.e., 15fx-group). Some left-sided breast cancer (LSBC) patients in both groups were treated with the DIBH protocol. Patients with bilateral breast cancer, with lymph node and chest wall RT were excluded from this study. This study was approved by the Iridium Netwerk ethics committee in June 2020 as a project for QA in healthcare. Patient consent was waived by the institute for this retrospective study.

2.2. Treatment delivery and verification

All patients were immobilized using breast board arm supports and treated with two tangential 6 MV dynamic IMRT photon beams. In order to ensure precise and reproducible patient setup, online and offline correction strategies were applied.

In the 5fx-group, each breast cancer patient was treated with the online IGRT protocol due to the short length of the treatment course to reduce systematic and random setup errors and identify the day-to-day variation. This daily online IGRT protocol included comparing orthogonal kV-kV images with digitally reconstructed radiographs (DRRs) generated from planning CT images. Immediate corrective action prior to each treatment fraction was performed by automated adjustment of the treatment couch in three dimensions when the shift exceeded the action level of 3 mm. After the couch corrections, a tangential MV image was acquired for final verification of treatment localization. In addition, EPID-based integrated transit dose images were acquired for each treatment fraction. Those were automatically retrieved via Digital Imaging and Communications in Medicine (DICOM) and analysed in PerFRACTION™ (part of SunCHECK™, Sun Nuclear Corporation) using a local gamma analysis with a threshold of 20%, a dose difference (DD) of 7%, a distance to agreement (DTA) of 6 mm and a passing tolerance level of 90% [15,16]. The fraction analysis was performed based on the average value of passing tolerance level of all beams. Gamma parameters for this EIVD were empirically determined along with an analysis of causes and actions taken for FFs, demonstrating that the system was sensitive enough to detect various types of errors and deviations as reported by Bossuyt *et al.* [16] in their first report. A local gamma analysis was performed because global analysis masked some problems [32], and the Planning Target Volume (PTV) margin of 6 mm was chosen as distance tolerance, a patient shift within the PTV margin being considered as clinically acceptable, as described in ref. [16]. The gamma index used was considered clinically relevant in avoiding too many false negatives and false positives [16].

In the 15fx-group, each breast cancer patient was treated with the offline IGRT correction according to our NAL protocols. The kV-kV images were acquired on the first 3 days of the treatment, then the mean setup errors were calculated and compared to a predefined threshold of

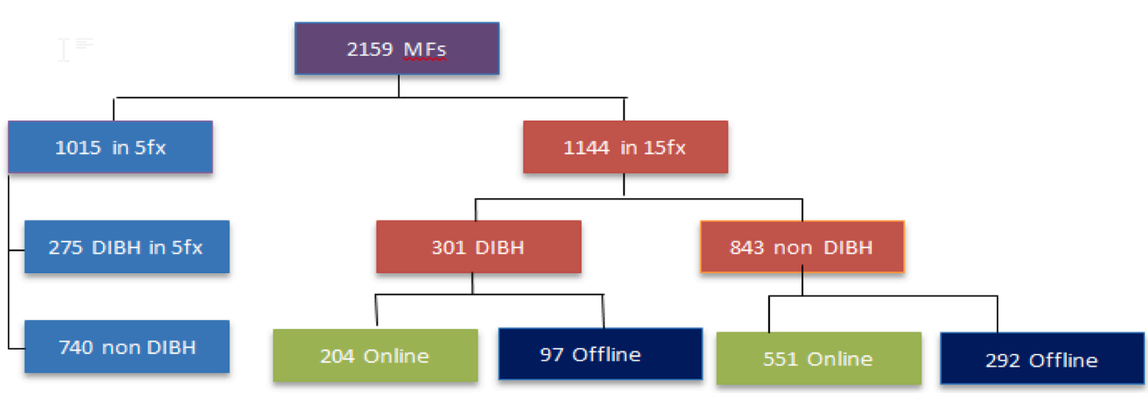

Fig. 1. Schematic overview of the number of EIVD measurements in the DIBH/non-DIBH 5fx-group (online IGRT) in light blue color and DIBH/non-DIBH 15fx-group in brown color (online IGRT in green color and offline IGRT in dark blue color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Details of statistical analysis between the 5fx-group and 15fx- group and between DIBH and non-DIBH subgroups (FFs and PFs; passed fractions).

Groups to compare	Categorical variable	x^2 (df,N)	P-value
5fx-group **vs.** 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 2159) = 47.5$**	**$P < 0.01$**
	Patient positioning	**$x^2(1, N = 2159) = 31.6$**	**$P < 0.01$**
	Breast swelling	**$x^2(1, N = 2159) = 4.6$**	**$P = 0.03$**
	Technical issues	**$x^2(1, N = 2159) = 9.6$**	**$P < 0.01$**
5fx-group **vs.** Online-IGRT 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 770) = 8.2$**	**$P < 0.01$**
	Patient positioning	$x^2(1, N = 770) = 0.2$	$P = 0.63$
	Breast swelling	$x^2(1, N = 770) = 0.01$	$P = 0.91$
	Technical issues	**$x^2(1, N = 770) = 13.5$**	**$P < 0.01$**
DIBH 5fx-group **vs.** DIBH 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 576) = 7.0$**	**$P < 0.01$**
	Patient positioning	**$x^2(1, N = 576) = 6.6$**	**$P = 0.01$**
	Breast swelling	$x^2(1, N = 576) = 0.1$	$P = 0.73$
	Technical issues	$x^2(1, N = 576) = 0.9$	$P = 0.34$
DIBH 5fx-group **vs.** Online-IGRT DIBH 15fx-group	EIVD MFs (FFs, PFs)	$x^2(1, N = 479) = 4.3e^{-4}$	$P = 0.98$
	Patient positioning	$x^2(1, N = 479) = 0.04$	$P = 0.85$
	Breast swelling	$x^2(1, N = 479) = 1.5$	$P = 0.22$
	Technical issues	$x^2(1, N = 479) = 2.7$	$P = 0.10$
non-DIBH 5fx-group vs. non-DIBH 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 1583) = 40.5$**	**$P < 0.01$**
	Patient positioning	**$x^2(1, N = 1583) = 24.9$**	**$P < 0.01$**
	Breast swelling	**$x^2(1, N = 1583) = 5.1$**	**$P = 0.02$**
	Technical issues	**$x^2(1, N = 1583) = 8.8$**	**$P < 0.01$**
non-DIBH 5fx-group **vs.** Online-IGRT non-DIBH 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 1291) = 9.7$**	**$P < 0.01$**
	Patient positioning	$x^2(1, N = 1291) = 0.2$	$P = 0.66$
	Breast swelling	$x^2(1, N = 1291) = 0.6$	$P = 0.44$
	Technical issues	**$x^2(1, N = 1291) = 12.6$**	**$P < 0.01$**
DIBH 5fx-group vs. non-DIBH 5fx-group	EIVD MFs (FFs, PFs)	$x^2(1, N = 1015) = 0.9$	$P = 0.35$
	Patient positioning	$x^2(1, N = 1015) = 3.7 e^{-4}$	$P = 0.99$
	Breast swelling	$x^2(1, N = 1015) = 0.4$	$P = 0.52$
	Technical issues	**$x^2(1, N = 1015) = 4.5$**	**$P = 0.03$**
DIBH 15fx-group vs. non-DIBH 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 1144) = 6.2$**	**$P = 0.01$**
	Patient positioning	$x^2(1, N = 1144) = 0,4$	$P = 0.55$
	Breast swelling	$x^2(1, N = 1144) = 0.5$	$P = 0.49$
	Technical issues	**$x^2(1, N = 1144) = 10.6$**	**$P < 0.01$**
Online-IGRT DIBH 15fx-group vs. Online-IGRT non-DIBH 15fx-group	**EIVD MFs (FFs, PFs)**	**$x^2(1, N = 755) = 6.8$**	**$P < 0.01$**
	Patient positioning	$x^2(1, N = 755) = 0.01$	$P = 0.94$
	Breast swelling	$x^2(1, N = 755) = 1.5$	$P = 0.22$
	Technical issues	**$x^2(1, N = 755) = 8.5$**	**$P < 0.01$**

3 mm, if this mean value exceeded the threshold, then a correction was performed on the 4th day and for all subsequent fractions. Furthermore, EPID-based integrated transit dose images were acquired on the first 3 days of treatment and weekly thereafter. If a measured fraction did not pass the gamma analysis, additional kV-kV, MV and transit dose images were acquired the next day. The fractions where pre-treatment kV-kV imaging was performed to verify (and correct if necessary) positioning were classified as a subgroup of the 15fx-group (i.e., Online-IGRT 15fx-group).

The influence of the Deep Inspiration Breath Hold (DIBH) technique on patient setup accuracy was also investigated in both the 5fx-group and 15fx-group. Subgroups of the 5fx-group (i.e., DIBH 5fx-group) and 15fx-group (i.e., DIBH 15fx-group) were formed with 55 LSBC patients each. The fractions where pre-treatment kV-kV imaging was performed to verify (and correct if necessary) positioning were classified as a subgroup of the DIBH 15fx-group (i.e.; Online-IGRT DIBH 15fx-group). Breast cancer patients not treated with DIBH technique were classified as patients in the non-DIBH 5fx-group and the non-DIBH 15fx-group.

2.3. *Outcome assessment*

The 2D gamma analysis results of the EIVD were retrieved from the database and a retrospective assessment was performed by evaluating comments related to the failed fractions (FFs) from both medical physicists and radiation oncologists in the software application and patient file. The deviations and errors detected are reported in terms of failed fractions (FFs), not passing the tolerance level. All causes of deviations were investigated and classified in 3 main categories: (1) patient positioning; (2) technical issues (i.e. wrong imager position, beam interrupted and imager calibration) and (3) breast swelling. For each failed fraction, only a single specific cause was assigned. If a failure was due to more than one reason, the cause with the largest contribution to the failure was assigned [15,16]. The breakdown of patient categories including the total number of measured fractions in each group (DIBH/non-DIBH) is shown in Fig. 1.

A total of 2159 measured fractions (MFs) of EIVD were analysed: 1015 MFs in the 5fx-group and 1144 MFs in the 15fx-group. Of the latter group, 755 had been treated with an online IGRT protocol (i.e. Online-IGRT 15fx-group). In the subgroups, a total of 576 MFs of EIVD were analysed in LSBC patients treated with DIBH technique: 275 in the DIBH 5fx-group and 301 in the DIBH 15fx-group, of which 204 had been treated with an online IGRT protocol (i.e. Online-IGRT DIBH 15fx-group). In the non-DIBH cohorts, 1583 MFs of EIVD were analysed: 740 in the non-DIBH 5fx-group and 843 in the non-DIBH 15fx-group, of which 551 had been treated with online IGRT protocol (i.e. Online-IGRT non-DIBH 15fx-group).

2.4. *Statistical analysis*

A Chi-Square test for two independent samples was used to test for significance of differences in EIVD measurements, in patient positioning, breast swelling and technical issues between the groups. The statistical analysis also included the evaluation of the P-value, degrees of freedom and sample sizes. A P-value < 0.05 was considered a statistically significant difference.

3. Results

Significant differences were found between the 5fx-group and the 15fx-group (Table 1). In the 5fx-group 3.8% of fractions failed compared to 12.0% in the 15fx-group. Reported causes for these FFs were classified into patient positioning (7.4%), technical issues (3.1%) and breast swelling (1.4%) in the 15fx-group, compared to 2.2%, 1.2% and 0.5% in the 5fx-group respectively. However, between the 5fx-group and the online-IGRT 15fx-group significant differences were found only in technical issues (Table 1). In the online-IGRT 15fx-group 6.9% of

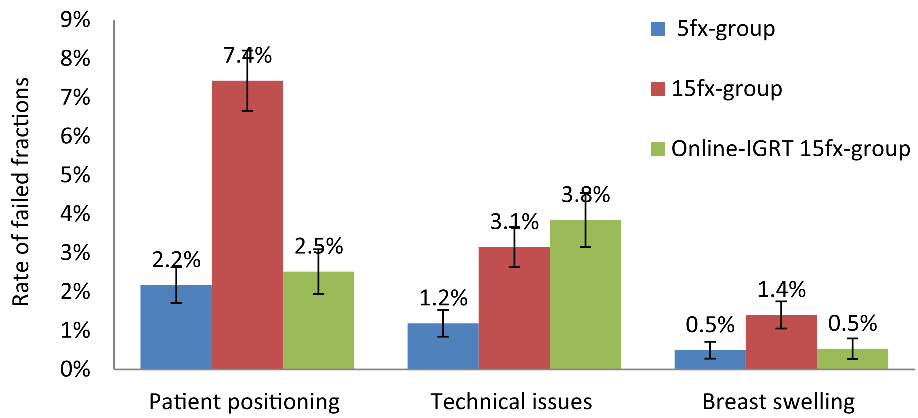

Fig. 2. Causes of failed fractions in the 5fx-group, 15fx-group and online-IGRT 15fx-group: patient positioning, technical issues and breast swelling.

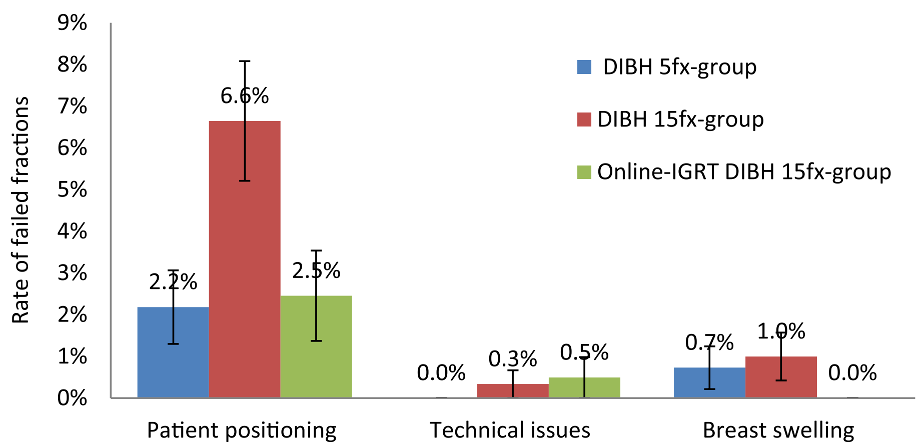

Fig. 3. Causes of failed fractions in the DIBH subgroups: patient positioning, technical issues and breast swelling.

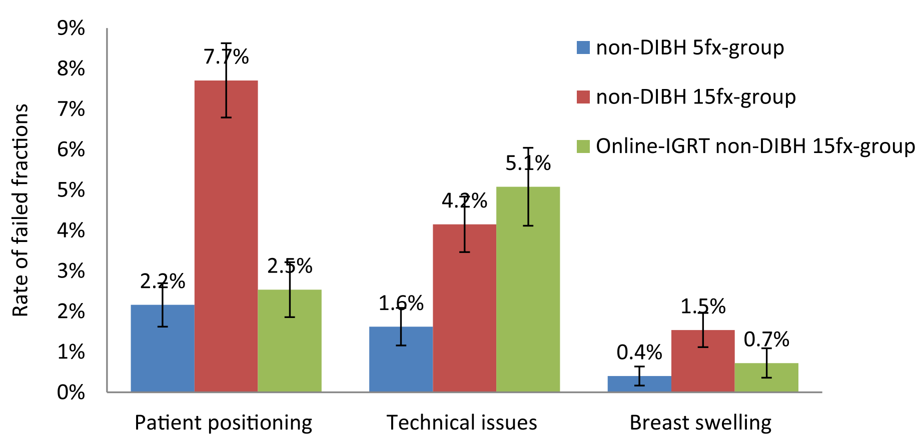

Fig. 4. Causes of failed fractions in the non-DIBH subgroups: patient positioning, technical issues and breast swelling.

fractions failed of which 2.5% were attributed to patient positioning, 3.8% to technical issues and 0.5% to breast swelling. Causes of FFs in the 5fx-group, 15fx-group and online-IGRT 15fx-group are shown in Fig. 2.

The same trend of results is visible in the DIBH and non-DIBH subgroups. Significant differences were found between the 5fx-groups and the 15fx-groups (DIBH/non-DIBH).

In the DIBH 5fx-group, 2.9% of fractions failed compared to 8.0% in the DIBH 15fx-group and 2.9% in the online-IGRT DIBH 15fx-group. Causes for these FFs were patient positioning (6.6%), technical issues (0.3%) and breast swelling (1.0%) in the DIBH 15fx-group, compared to 2.2%, 0.0% and 0.7% in the DIBH 5fx-group and 2.5%, 0.5% and 0.0% in the online-IGRT DIBH 15fx-group respectively. Significant differences were found only between the DIBH 5fx-group and the DIBH 15fx-group in patient positioning here (Table 1). Details of causes for the FFs in the DIBH 5fx-group, DIBH 15fx-group and online-IGRT DIBH 15fx-group are shown in Fig. 3.

In the non-DIBH 5fx-group, 4.2% of fractions failed compared to 13.4% in the non-DIBH 15fx-group and 8.3% in the online-IGRT non-DIBH 15fx-group. Causes for these FFs were patient positioning (7.7%), technical issues (4.2%) and breast swelling (1.5%) in the non-DIBH 15fx-group, compared to 2.2%, 1.6% and 0.4% in the non-DIBH 5fx-group and 2.5%, 5.1% and 0.7% in the online-IGRT non-DIBH 15fx-group respectively. Significant differences between the non-DIBH 5fx-group and the online-IGRT non-DIBH 15fx-group were found only in technical issues. The details of main causes of FFs in the non-DIBH 5fx-group, non-DIBH 15fx-group and Online-IGRT non-DIBH 15fx-group are shown in Fig. 4.

4. Discussion

This study demonstrated that treatment uncertainties encountered in breast cancer patients treated with UHFRT were smaller than for breast cancer patients treated with the standard HFRT (3.8% of failed fractions compared to 12.0%). The evaluation of the cause of the FFs indicated that there was a significant influence of patient positioning on setup accuracy and reproducibility. The effect of online/offline IGRT protocols and the DIBH protocol was investigated and showed that there was a significant decrease of deviations and errors using a daily IGRT verification protocol. The effect of the shorter treatment schedule on breast swelling was negligible.

Treatment uncertainties were evaluated using an electronic portal imaging device (EPID)-based in-vivo dosimetry (EIVD). Daily automated EIVD (forward projection approach) became the reference standard in UHFRT for breast cancer in our department because of short fraction schedules (26 Gy in 5 fractions) and high doses per fraction (5.2 Gy). In the 5fx-group, which was treated with the daily online IGRT correction protocol, only 3.8% of fractions failed 2D gamma criteria, of which 1.2% were false positive (FP) results compared to 12% of failed fractions, of which 3.1% were FP results in the 15fx-group treated with NAL offline IGRT correction protocol. There was a decrease for all causes in the 5fx-group compared to the 15fx-group and the online-IGRT 15fx-group. The difference between the 5fx-group and the online-IGRT 15fx-group, however, was not statistically significant for breast swelling and patient positioning suggesting that the daily online IGRT protocol might be the main explanation of superior results in the 5fx-group. The technical issues were mainly related to wrong imager position and in the 5fx-group this rate was lower because all patients were treated more recently following an introduction of improved imager shifting protocols. This implies that the daily online IGRT correction protocol significantly contributes to the reduction of setup and anatomical uncertainties compared with NAL offline IGRT correction protocol. It has been reported that offline IGRT strategies act on systematic effects while online IGRT strategies act on both systematic and random effects [33,22]. Zeidan *et al.* concluded that residual setup errors were reduced with increasing frequency of IGRT during the course of RT [34]. However, the benefits of daily IGRT need to be balanced against the costs, added time, doses and institutional-based PTV margins. Additionally, our results showed that residual setup errors remain present after the daily online IGRT correction because rigid registration fails to correct target deformation and anatomical motion of normal tissues and target during treatment [35].

NAL offline IGRT protocol lacks the capacity to mitigate residual errors as it employs imaging only during the first few fractions of the treatment. This approach may become sub-optimal in case of time trends in the displacement of patient. However, in e-NAL offline IGRT correction protocol, a weekly follow-up measurement can reduce residual uncertainties [36], at the cost of a higher frequency of imaging sessions and thus resulting in larger workload and imaging dose than the NAL protocol. Our EIVD analysis for the 15fx-group indicated that by acquiring daily online IGRT most deviations due to breast swelling and patient positioning would remain within tolerance level, and the number of FFs might be reduced to the level of the 5fx-group. This suggests treatment uncertainties in the 15fx-group would become comparable to the 5fx-group, if daily online IGRT would be used.

The combined effects of positioning errors and breathing motion can also introduce significant deviations. From Figs. 3 and 4, a significant decrease of FFs due to patient positioning is observed in both the DIBH and non-DIBH 5fx-group (2.2%/2.2%) compared to 6.6% and 7.7% in the DIBH and non-DIBH 15fx-group respectively. However, this significant difference in patient positioning is not observed between the DIBH/non-DIBH 5fx-groups and the online-IGRT DIBH/non-DIBH 15fx groups, suggesting that the daily online IGRT protocol might again be the main explanation of superior results.

Statistically significant differences were found between the DIBH 15fx-group (8.0% of FFs) and the non-DIBH 15fx-group (13.4% of FFs), suggesting that the combination of the DIBH and daily online IGRT protocol might reduce setup and organ motion residual uncertainties. However, further analysis between the DIBH and non-DIBH groups showed that there was no statistically significant difference in patient positioning or breast swelling suggesting that the use of the DIBH protocol does not have any significant influence on setup accuracy and reproducibility. There was only a statistically significant difference in technical issues. This was due to the type of machine used. All the DIBH patients were treated on new generation machines, while most of the non-DIBH patients were treated on old generation machines experiencing more calibration and imager position problems, and incomplete acquired images.

In conclusion, two-dimensional EIVD demonstrated that UHFRT for breast cancer results in less failed fractions compared to standard HFRT. A large proportion of this decrease could be explained by the use of a daily online IGRT correction protocol. Subsequently, the combined use of DIBH technique and daily online IGRT protocol could not assist in a larger reduction of residual uncertainties.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors have an on-going scientific collaboration with Sun Nuclear Corporation.

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