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Original paper

Breast intraoperative electron radiotherapy: Image-based setup verification and in-vivo dosimetry

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ABSTRACT

Introduction: Single fraction nature of intraoperative radiotherapy highly demands a quality assurance procedure to qualify both beam setup and treatment delivery. The aim of this study is to evaluate the treatment setup during breast intraoperative electron radiotherapy (IOERT) and in-vivo dose delivery verification.
Materials and methods: Twenty-five breast cancer patients were enrolled and setup verification for each case was performed using C-arm imaging. The received dose by surface and distal end of target was measured by EBT2 film. The significance level of difference between obtained dosimetry results and predicted ones was evaluated by the T statistical test.
Results: Acquired C-arm images in two different oblique views revealed any misalignment between the applicator and shielding disk. The mean difference between the measured surface dose and expected one was 1.8% ± 1.2 ($p = 0.983$) while a great disagreement, 11.1% ± 1.5 ($p < 0.001$), was observed between the measured distal end dose and expected one. This discrepancy is mainly correlated to the backscattering effect from the shielding disk. Target depth nonuniformities can also contribute to this remarkable difference.
Conclusion: Employing the intraoperative imaging for IOERT setup verification can considerably improve the treatment quality. Therefore, it is suggested to implement this imaging procedure as a part of treatment quality assurance. Favorable agreement between the predicted and measured surface doses demonstrates the applicability of EBT2 film for dose delivery verification. The results of in-vivo dosimetry showed that the electron backscattering from employed shielding disk can affect the received dose by the distal end of tumor bed.

1. Introduction

As reported by several studies [1–4], about 80% of breast cancer reoccurrences is located inside the index quadrant. Therefore, for small and early-stage breast cancer, partial breast irradiation (PBI) can be considered as an alternative method to whole-breast radiation therapy (WBRT). Intraoperative electron radiotherapy (IOERT) is one of the interested methods for partial breast irradiation (PBI) [5–8]. This technique refers to the administration of a high single dose to the remaining tumor bed after breast-conserving surgery (BCS) using an electron beam. The prescribed dose in this method can change according to the followed strategy, boost or radical one, for patient treatment [9–11].

IOERT is commonly done using mobile dedicated linear accelerators such as Mobetron, NOVAC, and LIAC that have a variable range of electron beam energies (3–12 MeV) and use dedicated cylindrical applicators for electron beam collimation and dose delivery [12–15].

After the tumor resection in this method, the underlying healthy organs such as lung and heart (in the case of left breast) are spared from target volume (tumor bed) through dedicated shielding disk. To this end, the surgeon will place a shielding disk between the distal end of the tumor bed and pectoralis muscle. This shielding disk is usually a

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double-layers one which can be made of different materials [15–19]. Then, the depth of the reconstructed target over the shielding disk is measured by a needle and electron beam energy is selected based on the measured depth. Finally, the applicator is located on the target and attached to the accelerator head through the docking procedure (hard or soft docking based on the type of employed dedicated IOERT machine [20]) and prescribed dose is delivered to the patient. The size of employed applicator and shielding disk is selected according to the actual size of the tumor bed after the surgery.

Breast IOERT can benefit from several aspects including direct target visualization during the treatment, shielding and sparing the organs at risk (OARs) from the incident electron beam and noticeable improvement in patient quality of life. Meanwhile, some difficulties such as irregular irradiation surface, accidental errors in the applicator and/or disk alignments and wound fluid accumulation on the target are associated with this treatment modality [21–24]. The effects of these perturbations can be serious regarding the single fraction nature of this treatment technique and lack of an image-based treatment planning procedure. As a result, development of a quality assurance program to evaluate the actual received dose to the target area and certify the proper alignment of shielding disk and applicator alignments is a mandatory issue during the breast intraoperative electron radiotherapy.

The aim of current study is to introduce a simple and reliable procedure for breast IOERT setup verification based on on-line intraoperative C-arm imaging and direct in-vivo dosimetry at the target reference points including surface and distal end of the target (tumor bed) using Gafchromic EBT2 film.

2. Materials and methods

2.1. Patient selection, dose prescription, and irradiation

25 patients with different types of breast cancer including invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS), which had the required indications, were selected for IOERT. All of the patients were informed and have given their consent to be involved in the current study. Furthermore, it should be mentioned that our ethical policy was based on Helsinki declaration principles.

All of the patient irradiations were performed by a dedicated LIAC 12 model (Sordina, SpA, Italy) with nominal electron energies of 6, 8, 10 and 12 MeV. In 36% of cases (9 patients), patients were undergone to the radical treatment (21 Gy prescribed dose) while the remaining cases (16 patients) were treated with boost strategy (12 Gy prescribed dose, except on case of 13 Gy according to the radiation oncologist opinion). Based on the target thickness, isodose prescription ranged from 86% to 90% to satisfy the target coverage requirements. All of the enrolled patients were irradiated by 8 MeV electron beam. The employed Perspex applicators were flat based ones with the diameter of 4–7 cm which were connected to the patient through the hard-docking mechanism.

3. Setup verification

One of the very important issues in breast IOERT is the proper alignment of the radiation field (applicator) and shielding disk respect to each other. Eventual shifts in the applicator and/or disk during the docking procedure can introduce large and irreparable errors to intraoperative radiotherapy. These misalignments can lead to both missing of the target area and over-irradiation of surrounding and underlying normal tissues.

In order to verify the treatment setup during breast IOERT, two C-arm fluoroscopic images were acquired after the docking procedure at two different views and position of applicator edge respect to the shielding disk was visually checked. The employed shielding disk in this study was a double-layer one which was composed of 0.3 cm thickness

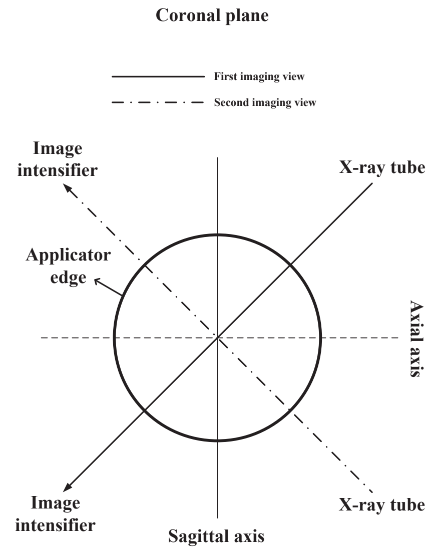

Fig. 1. Schematic diagram of employed C-arm imaging views for setup verification during the breast IOERT.

of Polytetrafluoroethylene (PTFE) as the upper layer and 0.3 cm thickness of Stainless Steel as the lower layer (manufactured by Sordina Company) [19]. The upper layer (low atomic number layer) is always faced to the incident electron beam.

To this end, a Ziehm Vision 8000 C-arm fluoroscopic system (Ziehm Imaging GmbH, Germany) was used to acquire the required C-arm images. Regarding the placement of applicator on the patient body and practical limitation in imaging at axial and sagittal views, the required images for setup verification were obtained in left-anterior oblique and right-anterior oblique views. The alignment of C-arm for intraoperative imaging at two above mentioned views is schematically shown in Fig. 1.

An actual C-arm arrangement inside the operating room for treatment setup verification is shown in Fig. 2.

4. In-vivo dosimetry

Checking the delivered dose to the target area during the breast IOERT is a quite mandatory issue considering the irregular treatment surface and fluid accumulation on the top surface of tumor bed (buildup effect) [21]. Due to the independent response to beam energy, incidence angle, dose rate and negligible perturbation inside the radiation field [25], the Gafchromic EBT2 film (ISP, USA) was used for in-vivo dosimetry.

The films were initially calibrated inside the water and at the reference depth of 9 MeV electron beam from a conventional Varian 2100C/D accelerator.

To measure the received dose by the target surface, a $2 \times 2\,cm^2$ film piece was wrapped inside a sterile plastic envelope and placed on the top surface center of tumor bed by the surgeon (as shown in Fig. 3). All of the safety requirements were followed to keep the sterilized conditions inside the operating room.

The received dose to the distal end of tumor bed was measured through positioning a circular EBT2 film piece on top of the employed shielding disk with the same size. This arrangement can be also used to obtain the radiation field projection on the distal end of the target. As shown by Fig. 4, both film and shielding disk were placed inside a sterile plastic envelope.

All of the irradiated films (both calibration and dosimetry films) were readout 24 h after exposure to have a stabilized polymer growth inside the film active layer [26,27]. Films were scanned in the landscape position using a Microtek 9800XL flatbed scanner in transmission mode and saved as Tagged Image File Format (TIFF). To indicate the

Fig. 2. Alignment of C-arm imaging system inside the operating room for treatment setup verification.

Fig. 3. Employed clinical setup for surface dose measurement. The films were wrapped inside a sterile plastic envelop and positioned on the surface of treatment target.

right direction for film scanning (landscape orientation) some arrows were drawn at the corners of the film which showed us the scanning direction after film exposure. The scanner was turned on 30 min prior to scans in order to minimize the effects of scanner warm up on film readout [28]. All of the scans were performed in RGB mode (16 bit per channel) and spatial resolution of 72 dpi (dots per inch) [29,30]. Due to the high delivered doses in IOERT (more than 10 Gy), the response of irradiated films was obtained and processed in the green channel [31]

Fig. 4. positioning the a circular piece of EBT2 film on the top surface of shielding disk and wrapping them inside a sterile plastic envelop for in vivo dosimetry at the distal end of tumor bed.

by a hand-written program developed by MATLAB software (MathWorks, Natick, MA). Finally, the film response (in terms of net-OD) was converted to the absorbed dose by means of obtained calibration curve. It should be mentioned that a region of interest (ROI) containing 25 × 25 pixels at the center of each film irradiated area was considered for film readout to minimize the introduced artifacts due to the cutting process near the film edge.

The measured dose by employed films was also compared with the expected dose at the surface and distal end of the target and significance level of their difference was determined by T-test using Minitab16 statistical software (Minitab Inc.) P-values greater than 0.05 were considered as not significant difference.

5. Results and discussion

The results of intraoperative imaging and acquired C-arm image in wrong treatment setups, for a typical contributing patient, is shown in Fig. 5.

As it can be seen from Fig. 5, the misalignments in the applicator and/or disk position can be satisfactorily detected by such on-line imaging. As shown here, the applicator is shifted respect to the shielding disk. The average shift values between the applicator and shielding disk were about 1.8 cm ± 5% (the distance between the applicator center and shielding disk one).

On the other hand, Fig. 6. A and 6. B illustrate the right treatment setup in two different oblique views for the same patient after correcting the detected displacements in Fig. 5.

The most important factor in such occurred misalignments is slipping the applicator edge on the breast glandular tissue during the docking procedure. This issue is mainly due to the soft and flexible nature of breast glandular tissue as well as potential bleedings and fluid accumulation on the target surface after the surgery. Furthermore, the shielding disk can also be moved due to the applicator pressure on the patient body. These misalignments can finally lead to the following problems:

- Missing and under-dosage of the target area as well as the over-exposure of surrounding and underlying healthy tissues due to the displacements and unexpected shifts of employed electron applicator.
- Over-exposure of surrounding and underlying healthy tissues

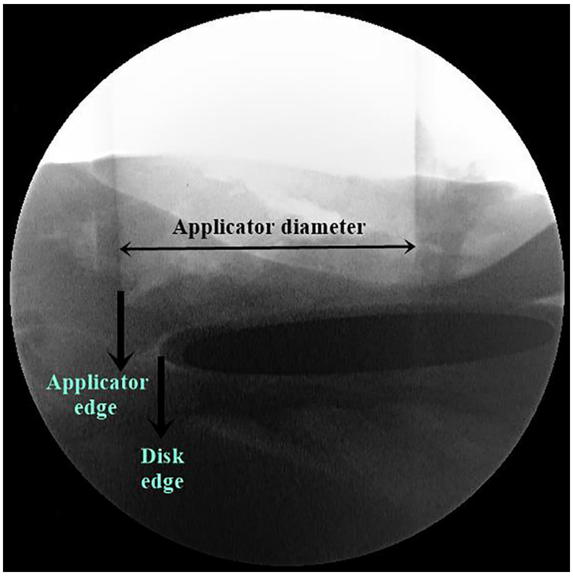

Fig. 5. Obtained C-arm image which indicated the wrong treatment setup. As shown here, the radiation field and shielding disk are not properly aligned respect to each other.

because of undesirable movements of shielding disk.

Regarding the high prescribed doses in IOERT, these mismatches can lead to serious biologic damage to the normal tissues such as increased risk of necrosis or secondary cancer in such organs. Intraoperative C-arm imaging can reveal the occurred slipping and unwanted movements of the applicator and/or shielding disk by online checking the applicator position respect to the disk in two perpendicular views. Correction of such setup misalignments can considerably improve the treatment quality.

At first glance, it seems that the surgeon can detect these misalignments by manual checking of applicator position respect to the underlying shielding disk using a needle. But the obtained results following this approach were not clinically acceptable. For example, two samples of circular irradiated films which were located at the distal end of the tumor bed are shown in Fig. 7 for two different patients. The left side film is obtained after the manual setup verification while the right one is obtained following the online image-guided setup verification using intraoperative C-arm imaging.

As presented in Fig. 7.A, a considerable fraction of intraoperative radiation field stays outside the target and shielding area when the treatment setup is manually checked by the surgeon. On the other hand, as shown in Fig. 7.B, a desirable matching is obtained between the radiation field and shielding area through employing the intraoperative imaging for treatment setup evaluation.

The most important problem during intraoperative imaging is the proper alignment of C-arm relative to the applicator. Our experience in this regard showed that when the connecting line of image intensifier center and X-ray tube is perpendicular to the applicator central axis, interested areas in intraoperative radiotherapy including tumor bed, applicator edge, and shielding disk would be fully involved in acquired images.

The total required time for C-arm imaging is about 10 min, provided the applicator and shielding disk setup would be right. But, if the user finds a shift in treatment setup, it is necessary to remove the applicator and correct the shielding position and then the C-arm imaging should be repeated, so it takes more time for online image-based setup verification. Furthermore, C-arm imaging can also lead to undesired dose to organs at risk like lung and heart.

Besides the online C-arm imaging which is introduced in the current study, other setup verification methods such as needle-based verification, ultrasound imaging, and development of dedicated mechanical fixation tools have also been introduced in this regard [24,32]. Although the needle-based setup verification is fast, this method is not accurate according to our experiences in manual setup verification with the needle. Ultrasound imaging for IOERT setup verification is an accurate method [32]. Although, ultrasound imaging is considered as a non-invasive method for breast IOERT setup verification, it demands dedicated and specific equipment for imaging inside the operating room. In addition, more time is needed for setup verification in this method respect to employing a needle for such purpose. Employing dedicated mechanical fixation tools can improve the accuracy of breast IOERT setups [24], but this method needs to design and construct the intended facility for setup verification. Furthermore, using this mechanical device may also complicate the placement of the shielding disk inside the patient's body as well as the docking procedure of the accelerator head to the patient's body (especially in the hard-docking mechanism).

The results of in-vivo dosimetry in measuring the surface dose for different patients are reported in Table 1.

As presented in this Table, the mean difference between the measured dose and the expected dose is equal to 1.8% ± 1.2 (one standard deviation). It should be mentioned that the expected surface doses were obtained from Monte Carlo based calculated PDDs by EGSnrc Monte Carlo code. According to the results of performed statistical analysis (two sample T-test), the difference between the obtained results was not significant (p-value = 0.983) which indicates the good agreement between the in-vivo dosimetry results and expectable received dose to the surface. The maximum difference between the obtained results was

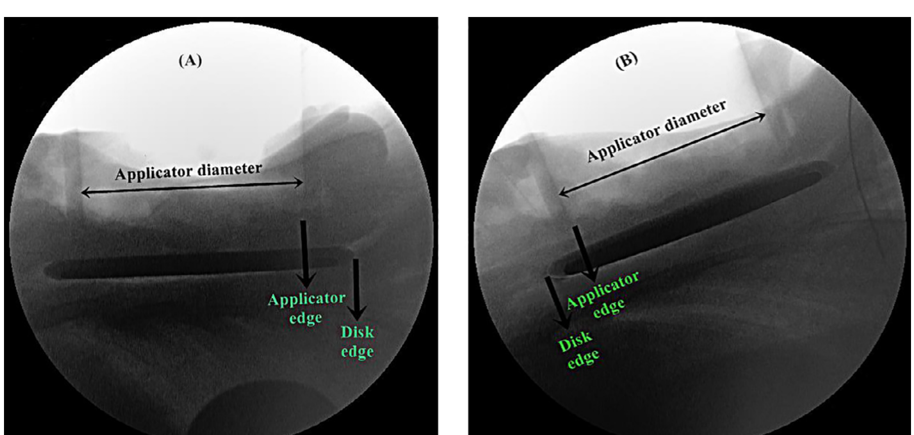

Fig. 6. Obtained treatment setup in two different imaging views (A and B) after correcting the eventual misalignments during the docking procedure.

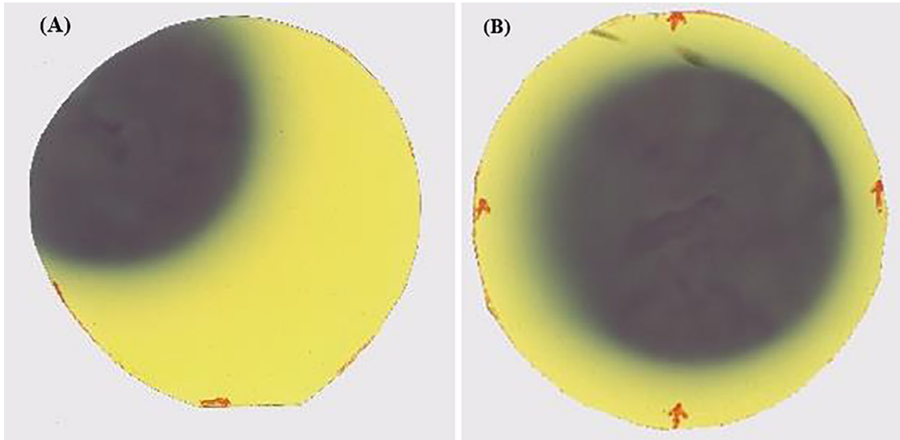

Fig. 7. Projection of the radiation field on Gafchromic EBT2 film at the distal end of target. (A) Is related to the patient irradiation after the manual setup verification and (B) shows the obtained irradiation result after an image based setup verification inside the operating room.

equal to 4.5% which is in accordance with the recommended dose uncertainties up to 5% in Gafchromic EBT2 based film dosimetry[25].

Dosimetry of target surface in breast IOERT is performed by Ciocca et al.[33,34] using MD-55-2 Gafchromic film and micro-MOSFET detectors. As reported by these studies, the mean difference between measured and expected dose was obtained as 1.8% and 0.6% with film and MOSFET dosimetry, respectively. Consorti et al. [21] also measured the surface dose in breast IOERT through in-vivo MOSFET dosimetry. Their results showed that the maximum difference between the measured and predicted dose was about 5%.

The received dose by the surface of the target in the breast IOERT was also measured by Petoukhova et al. [35] by means of both Gafchromic EBT2 film and MOSFET dosimeters. The results of this in-vivo dosimetry showed that the difference between the measured and expected surface dose is equal to 1.7% and 0.7% for EBT2 film and MOSFET dosimetry, respectively.

Although, in-vivo dosimetry approach was followed by our study and above-mentioned literature as a part of quality assurance (QA) in the breast IOERT, the main difference between our research and mentioned references [21,33–35] was introducing a complementary QA procedure through online C-arm imaging for setup verification in breast IOERT.

The received dose by the distal end of tumor bed for each enrolled patient is presented in Table 2.

As shown in Table 2, considerable discrepancies were observed between the in-vivo measured dose and expected values; so that the mean difference between the results was obtained as 11.1% ± 1.5 (one standard deviation). This difference was quite significant based on the performed statistical analysis (paired T-test, p-value < 0.001). The maximum and minimum difference between the measured and expected dose was equal to 14.3% and 8.3%, respectively. No considerable human error (such as wrong setting of treatment parameters, docking an incorrect applicator size and erroneous Monitor Unit (MU) calculation) or variation of IOERT machine output was detected during the treatment procedure screening which can be ascribed to this remarkable discrepancy.

The main reason for this large difference is the presence of shielding disk. Furthermore, both the wrong determination of target thickness

Table 1
Treatment summary and results of in vivo film dosimetry in measuring the surface dose in breast intraoperative electron radiotherapy.

Pat. no	Energy (Mev)	App. Diameter (cm)	Target thickness (cm)	PDD (%)	Prescribed dose (Gy)	Isodose prescription (%)	Predicted dose (Gy)	Measured dose (Gy)	Relative difference (%)
1	8	5	1.5	87	13	90	12.6	12.9	2.3
2	8	6	1.7	87	12	90	11.6	11.1	−4.5
3	8	5	1.7	87	21	86	21.2	21.2	0
4	8	5	1.9	87	12	89	11.7	11.7	0
5	8	5	1.5	87	21	86	21.2	21	−1
6	8	7	1.5	88	12	90	11.7	11.8	0.8
7	8	6	1.7	87	12	90	11.7	12	2.5
8	8	5	1	87	21	86	21.2	20.9	−1.4
9	8	7	1.5	88	12	90	11.7	11.5	−1.7
10	8	5	1.5	87	21	87	21	20.7	−1.4
11	8	6	2	87	12	90	11.6	11.7	0.9
12	8	4	1.4	87	12	90	11.6	12	3.3
13	8	4	1.5	87	21	87	21	21.4	1.9
14	8	7	1.9	88	12	90	11.7	11.7	0
15	8	6	1.6	87	12	90	11.6	11.4	−1.8
16	8	6	1.8	87	21	90	20.3	20	−1.5
17	8	5	1.6	87	12	90	11.6	11.2	−3.6
18	8	5	1.5	87	12	86	12.1	11.8	−2.5
19	8	6	2	87	12	90	11.6	11.5	−0.9
20	8	4	1.5	87	12	90	11.6	12	3.3
21	8	5	1.7	87	12	88	11.9	12.1	1.7
22	8	5	1.5	87	21	87	21	21	0
23	8	5	2.1	87	21	90	20.5	19.9	−3
24	8	6	1.5	87	21	87	21	21.7	3.2
25	8	6	1.8	87	12	90	11.6	11.4	−1.8

Table 2
Treatment summary and results of in vivo dosimetry at distal end of tumor bed in breast intraoperative electron radiotherapy.

Pat. no	Energy (Mev)	App. diameter (cm)	Target thickness (cm)	PDD (%)	Prescribed dose (Gy)	Isodose prescription (%)	Predicted dose (Gy)	Measured Dose (Gy)	Relative difference (%)
1	8	5	1.5	98	13	90	14.2	15.9	10.7
2	8	6	1.7	97	12	90	12.9	14.7	12.2
3	8	5	1.7	95	21	86	23.2	26.4	12.1
4	8	5	1.9	95	12	89	12.8	14.4	11.1
5	8	5	1.5	98	21	86	23.9	26.1	8.4
6	8	7	1.5	99	12	90	13.2	15.4	14.3
7	8	6	1.7	96	12	90	12.8	14.6	10.3
8	8	5	1	100	21	86	24.4	27.2	10.3
9	8	7	1.5	99	12	90	13.2	15	12
10	8	5	1.5	98	21	87	23.7	26.2	9.5
11	8	6	2	93	12	90	12.4	13.7	9
12	8	4	1.4	100	12	90	13.3	15.4	13.6
13	8	4	1.5	99	21	87	23.9	27	11.4
14	8	7	1.9	95	12	90	12.6	14.1	10.6
15	8	6	1.6	99	12	90	13.2	14.8	10.8
16	8	6	1.8	96	21	90	22.4	25.6	12.5
17	8	5	1.6	97	12	90	12.9	14.5	11
18	8	5	1.5	98	12	86	13.7	15.5	11.6
19	8	6	2	93	12	90	12.4	13.8	10.1
20	8	4	1.5	99	12	90	13.2	15	11.3
21	8	5	1.7	97	12	88	13.2	14.7	10.2
22	8	5	1.5	98	21	87	23.7	27	12.2
23	8	5	2.1	90	21	90	21	22.9	8.3
24	8	6	1.5	99	21	87	23.9	27.4	12.8
25	8	6	1.8	96	12	90	12.8	14.5	11.7

and its non-uniformities can also contribute to these observed discrepancies.

Backscattered electrons from the upper surface of shielding disk will further contribute to the received dose by the distal end of tumor bed and as a consequence, the absorbed dose increases in this region [15,16,19,22]. Since the backscattering effect is not considered during the manual treatment planning and Monitor Unit (MU) calculations, the discrepancy between the measured and calculated dose at the distal part of the target increases. As reported by Robatjazi et al. [19], the backscatter factor (BSF) of employed shielding disk in the current study (0.3 cm PTFE + 0.3 cm Steel) at the depth of 90% dose (R_{90}) of 8 MeV electron energy is equal to 8%. Therefore, an average increase of 8% respect to the predicted dose would be expected in received dose to the distal end of the target. Nevertheless, as reported in Table 2, the distal end of tumor in most of the cases is at the shallower depths of the corresponding R_{90} and therefore, the shielding disk is not exactly located at the R_{90} of incident electron beam. On the other hand, the percentage increase in received dose to the disk/target interface would be higher when this interface has been located at the shallower depths, as illustrated by Catalano et al. [16]. Therefore, it would not be irrational to observe greater discrepancies (above 8%) between the measured and expected doses.

Non-uniformities of target thickness at different regions as well as the wrong estimation of target thickness will change the isodose prescription level during the manual treatment planning procedure and as a result, the expected dose is not correctly calculated. Increasing the number of acquired thickness sample by the surgeon can minimize the introduced uncertainties in target thickness determination. In general, the BSF has different values depending on the target tissue thickness between applicator and shielding disk. Target tissue thickness is not homogeneous from practical experience so BSF is not fixed over film irradiated area. Insert a shielding disk, CT image acquisition and dosimetry calculation inside the operation room is the most precise IOERT dosimetry [36,37].

Severgnini et al. [23] also directly measured the received dose by the distal end of the target in breast IOERT using Gafchromic EBT3 film. The very large dose differences such as 39% reported by Severgnini et al., was not observed in our study. This large difference was due to the imperfect alignment between the applicator and shielding disk which was eliminated through intraoperative C-arm imaging in our study. Nevertheless, the average difference between our results was higher than those of Severgnini et al. which can be mainly attributed to the difference between employed shielding disks in these two studies. Severgnini et al. used a 1 cm thick disk made of PMMA + Copper in their study. As illustrated by Oshima et al. [18], PMMA + Copper disk has a negligible electron backscattering at R_{90} of different intraoperative electron energies. As a result, it can be expected that the contribution of backscattering effect in absorbed dose by the distal end of the target in our study would be higher and therefore, the difference between measured and predicted dose increments.

Although the passive response of Gafchromic film dosimetry and single fraction nature of IOERT make it not possible to correct the patient dose during the treatment, its response can be a caution for considering all of the possible uncertainties including the backscattering effect, breast tissue heterogeneities, and target depth non-uniformities which can affect the actual dose which should be delivered to the future patient.

6. Conclusion

The accuracy of breast intraoperative electron radiotherapy was evaluated through introducing a novel method based on C-arm intraoperative imaging for pre-irradiation setup verification and simultaneous in-vivo dosimetry at the surface and the distal end of the target.

The results of intraoperative imaging showed that employing this approach during breast IOERT can minimize any eventual misalignment during the treatment setup. Although the imaging procedure will extend the total treatment time (about 10 min based on our experience), but has an important role in treatment quality improvement viewpoint to the increment of tumor control probability through exact matching of radiation field to the target area and reduction of normal tissue complicated probability by effective sparing the surrounding and underlying normal tissues.

There was an acceptable agreement between the in-vivo measured and predicted surface dose, while a significant difference was observed between the measured and expected distal end dose which can be attributed to the presence of shielding disk and backscattering phenomenon from the upper part of the disk. In this regard, employing an optimum shielding disk composition (such as PMMA + Copper [18]) can minimize the backscattering effect from the disk.

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