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Skin dose assessment with treatment planning system (TPS) and skin reaction evaluation of early breast cancer patients treated via an intraoperative radiation therapy (IORT) device

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Abstract

Purpose: To assess skin dose and incidence of skin reactions in early breast cancer patients treated via Intrabeam™ intraoperative radiation therapy (IORT) device. *Materials and methods:* In total, 250 breast cancer patients treated with a single fraction of 20 Gy using 50 kV photon were recruited. The applicator to skin distance (ASD) was measured before the initiation of the radiation and the skin dose in each patient was accordingly calculated based on the treatment planning system (TPS). *Results:* The average skin doses calculated were equal to 7·91, 5·83, 3·96 and 2·14 Gy for 6–10, 10–15, 15–20 and 20–30 mm ASD values, respectively. It is noticeable that the skin doses could be lower than the TPS measurements up to 45%, mostly due to lack of backscatter radiation in breast tissue compared with the full scatter condition in the Zeiss water phantom. Finally, only three patients showed low-grade skin reactions 1 week after IORT. A review of the related literature also revealed the incidence of lower skin complications among patients treated via Intrabeam™ compared with MammoSite™ machine. *Conclusions:* The Intrabeam™ TPS did not seem to be very reliable for accurate skin dosimetry. However, breast cancer treatment using Intrabeam™ could result in fewer incidences of skin reactions than MammoSite™ machine.

Introduction

Background

Over recent years, most of physicians and patients are adopting the use of accelerated partial breast irradiation (APBI) for the treatment of breast cancer due to its acceptable outcomes reported by both patients and physicians.[1] In this respect, patients with early stage breast cancer (ESBC) who have also experienced breast conserving surgery (BCS) after sessions of whole breast irradiation are one of the target groups that can receive APBI.[2] After the BCS, the existence or absence of cancerous cells from the excised tumours can be ambiguous. Also, the presence of wound fluids in the tumour bed after the BCS is likely to bring about concerns regarding future recurrences.[2,3] Therefore, almost all patients will undergo additional treatments after the BCS to ensure the eradication of any residual tumour cells. Observations, in recent years, have also shown that the APBI can be considered more desirable than traditional whole breast radiation for the ESBC patients due to reduced treatment time and also better cosmesis (preservation of physical appearance).[4] Studies have similarly suggested that recurrences in breast cancer patients after the BCS can mostly occur in the index quadrant of their breast mass.[5] These observations have consequently raised the question whether the whole breast irradiation is necessary after the BCS for the prevention of recurrences or not. In fact, this procedure can lead to an increase in the possibility of further complications.[6] Following the APBI, unnecessary irradiation to normal adjacent tissues around the tumour bed is decreased; thus, the risk of further complications such as skin reactions can be lowered to a desirable level. The APBI is also regarded to be an accepted procedure compared with the conventional whole breast radiation therapy referring to the delivery of 50 Gy dose in 2 Gy fractions 5 days a week during 6 to 6·5 weeks. In return, the APBI refers to delivery of, for example, 32 Gy in about 2 weeks, which can facilitate the possible chemotherapy if needed.[2] Besides; the targeted intraoperative radiation therapy (TARGIT) refers to intraoperatively radiation therapy of cancer patients using low energy (50 kV) X-ray, which can get rapidly attenuated in the tissue surrounding the tumour bed.[3,7] The TARGIT can be also considered as a modified and still progressing approach of the APBI.

Some approaches of APBI delivery

Low-energy therapeutic X-ray machines mainly include Intrabeam™, Axxent™ and Papilon™ that are extensively used for breast cancer treatment due to possessing spherical applicators providing a good coincidence with the tumour bed with an acceptable adherence which can be important to prevent dosimetric uncertainties during the treatment.[8,9]

The purpose of this study was to evaluate the incidence of skin reactions among 250 breast cancer patients treated via Intrabeam™ device at Pastorno Hospital in the city of Mashhad, Iran, over 18 months. Actually, it should be noted that the Intrabeam™ treatment planning system (TPS) is used for skin dose measurement of each patient and the Radiation Therapy Oncology Group (RTOG) skin reaction grading system can be implemented for describing probable skin reactions of the treated patients. However, the present study particularly focused on physical aspects of Intrabeam™ TPS as a dose-measuring tool of the device. A comparison was also made between the results of the present study and some other investigations about skin reactions or other reverse treatment outcomes of breast cancer patients treated using the Intrabeam™ device or some other devices like the MammoSite™ radiation therapy system (Proxima Therapeutics Inc., Alpharetta, GA, USA).

The low-energy therapeutic X-ray machine, Intrabeam™ (Carl Zeiss Surgical, Oberkochen, Germany) has been also introduced in some previously published studies.[6,8,10–12] In summary, the system is able to produce low-energy photons through striking 40 μA current of accelerating electrons irradiated from an electron gun with a 40 or 50 keV of maximum energy to the concave end of a drift tube (probe) with 10 cm length and 3·2 mm diameter. The electrons are then guided via the hollow probe by two pairs of beam deflectors until striking the concave area at the probe end. Therefore, an isotropic distribution of photons with the maximum energy of 50 kV (or 40 kV) is expected to radiate from the probe tip by bremsstrahlung coincidence. The probe tip is also worn with a spherical applicator almost for breast therapeutic purposes. It should be noted that the spherical applicators are available with eight diameters between 1·5 and 5 cm with 0·5 cm increments which can provide an isotropic dose distribution around the applicator with rapid dose attenuation in terms of the inverse cube of distance. The given feature has been always considered as one of the most desirable characteristics of the Intrabeam™ device which leads to minimising unnecessary doses to normal adjacent tissues. As an example, heart and lung will not be exposed to significant amounts of radiation in breast treatments.[3] The possibility of launching the procedure in a normal operating theatre without having any additional structural shielding is a further advantage of the rapid beam attenuation.

Materials and Methods

Skin dose measurement and skin reaction evaluation of early breast cancer patients were performed, respectively, using the Intrabeam™ TPS and RTOG skin reaction grading system in this study. One of the objectives was to have an overall assessment of the effect of the treatment process on the incidences of skin reactions among patients. In addition, the function of the TPS as a dose-measuring instrument along with comparison of the incidence of skin reactions in patients treated with Intrabeam™ device and the MammoSite™ system were discussed.

In this regard, 250 ESBC patients, aged 33–86 years, treated with a single fraction of 20 Gy using 50 kV photon beam were selected. Then, the spherical Intrabeam™ applicators with a diameter range of 3 cm (for two patients) to 5 cm (for 131 patients) were used for intraoperatively treating the tumour bed after the tumour removal. Following the tumour excision by the surgeon, a purse string suture was made on the surgical cavity and the tumour depth was measured as the applicator to skin distance (ASD) for further skin dose calculations according to the TPS. Then, the applicator was placed within the breast to trigger the treatment. After the personnel exited from the operating room and a window lead apron was placed at the theatre room entrance, the radiation procedure was initiated by the physicist. Most of the patients received the treatment as a boost, but there were also some cases receiving it as radical or definitive treatment. The patients were then clinically evaluated 1 week after the treatment and before the external beam radiation therapy procedure initiation, in order to specifically evaluate the incidence of the intraoperative radiation therapy (IORT) related skin reactions. The patients' skin reaction evaluation was also performed using the RTOG grading system as mentioned.[13,14]

Results

The ASD values were measured between 6 and 30 mm with an average of 14·6 mm. The ASD for 13 patients was less than 10 mm; that was 10–15 mm for 107 patients and 15–20 mm for 62 patients, and finally 68 patients had an ASD range of 20–30 mm. The average skin dose for four ASD ranges was calculated between 1·38 and 9·08 Gy as illustrated in Table 1. The average skin dose of all patients was also calculated equal to 4·9 Gy. As shown, the first column of the table represented the ASD range in terms of mm, middle columns were associated with the number of patients treated with various applicator sizes and the mentioned ASD ranges, and the last column showed the average skin dose of patients. The average skin doses represented a downward trend with an increasing ASD, as shown in the Table 1. Absorbed skin doses are calculated according to Intrabeam™ TPS based on the measured ADS value and applicator size used for each patient. It is noteworthy to know that the TPS represented the depth dose data by half millimetre increments for each patient according to the applicator size and the source output. The mentioned data root in calibration data of the Intrabeam™ device was verified in periodic quality assurance using Zeiss water phantom and ion chamber (type PTW 23342 used for low-energy therapeutic beams).[7] Among all the patients, only three of them developed

Table 1. The data of the patients intraoperatively treated using Intrabeam™ device

	Applicator size (cm)					
ASD (mm)	3	3·5	4	4·5	5	Average skin dose (Gy)
6–10	–	2[a]	2	4	5	7·91
10–15	–	3	17	26	61	5·83
15–20	–	1	3	22	36	3·96
20–30	2	3	12	23	29	2·14

Note:
[a]Number of patients treated with each four ranges of ASD and various applicator sizes.
Abbreviation: ASD, applicator to skin distance.

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low-grade skin reactions with the RTOG 1 score 1 week after the IORT procedure in which, one of them received 9·08 Gy with 6 mm ASD and two other patients received 6·92 Gy both with 10 mm ASD.

Discussion

Measured skin doses

Measured skin doses mentioned in this study were obtained from the Intrabeam™ TPS, which were based on commissioning and quality assurance measurements using Zeiss water phantom. However, some considerations were required to be accurately considered as follows. Measuring the depth dose in Zeiss water phantom consisted of a full scatter condition due to its dimensions of $58 \times 40 \times 52$ cm which was filled up with 6 L of water.[7] The backscatter radiation also plays a significant role for dose deposition at this energy range.[15,16] In return, due to lack of tissue in a real treatment procedure, particularly for low ASD values, there is a considerable reduction of backscatter exposure compared with the procedure performed in the Zeiss water phantom. In that way, the lower the ASD or the less tissue around the applicator surface could lead to a reduction of backscatter radiation and subsequently under dose in the breast skin. According to a Monte Carlo study, this effect could lead to 20–40% dose reduction in comparison with measurements performed at corresponding distances in the Zeiss water phantom.[17,18] Furthermore, the higher density of the breast tissue compared with water[19] could lead to a steeper dose fall in a real treatment procedure. Such calculations showed 3–5% lower amounts of absorbed doses in tissues adjacent to the applicator surface compared with the corresponding distances in water.[9,17] Also, the inhomogeneous tissue of the breast could make much more dose measurement uncertainties somehow that the isotropic dose absorption could not necessarily occur in breast tissue similar to the dose measurements in quality assurance procedure in the Zeiss water phantom.[17] Considering these points, the measured doses using the Intrabeam™ TPS involved a huge uncertainty which could be up to 45%. In fact, there was so much pleasure about it, because the mentioned uncertainties led to a considerable dose reduction in the sensitive nearby tissues, particularly in the skin. In other words, the results of the present study verified this claim since only three patients showed low grade skin reactions. If that was not the case, most probably more cases of skin toxicities even with higher grades of complications would be observed. From another point of view, this issue would bring about some concerns about enough dose absorption in the target tissue and further probable recurrences of the malignancy.

Regarding the skin dose reduction in real procedures, particularly in shallow treatments due to lack of backscatter, wrapping the Intrabeam™ shield (equal to 0·1 mm lead)[7] over the breast during treatment could lead to a dose increase due to the more backscatter production.[9,17] In the same vein, it seemed that implementing at least 1 cm ASD[9,20,21] without wrapping any shields on the patients was enough for skin sparing, in case of proper personnel shielding availability like the lead apron at the entrance of the operating theatre.

According to the surgeon's declaration, a noticeable factor which could affect the ASD was the initial tumour region in the breast mass. In which, insertion of the applicator within the upper areas of breast could lead to a lower ASD value compared with areas around the nipple or the breast centre. Therefore, much attention is required to be paid to make the ASD at least 1 cm before the initiation of radiation for such cases. In addition, insertion of a wet piece of sterilised gauze between the applicator and the thin layer of breast tissue, before tightening the purse string suture, could protect the skin from receiving high dose radiation.[21,22]

A comparison between electronic and radionuclide brachytherapy

The incidences of skin reactions following breast cancer treatment using the Intrabeam™ device and the MammoSite™ system, each one respectively as representative of electronic and radionuclide brachytherapy systems, were compared as follows. Some studies about breast cancer treatment outcomes using the MammoSite™ therapeutic system have been published between 2005 and 2016 aimed to reveal treatment outcomes like skin reactions or any other possible complications following receiving 34 Gy at 1 cm depth per 10 fractions. Almost all of the authors have considered the MammoSite™ machine as a completely acceptable therapeutic system for treating breast cancer, which can be also promising.[4,23–25] In more detail, Sadeghi et al.[24] reported that 44% of 67 patients had experienced skin complications at various levels from erythema to moist desquamation. Vicini et al.[23] also reported good/excellent outcomes among 92% of 1,084 patients of an intra-institutional trial. Such outcomes included various factors like skin reactions, recurrence rates, developing infections in breast, etc. Besides, Cuttino et al.[25] observed skin reactions from erythema (40%) to moist desquamation (4%), infections (10%), telangiectasia (17%), hyperpigmentation (16%) and desquamation toxicity from merely palpable changes (28%) to surgical interventions (2%) among 483 patients treated with MammoSite™ machine between 2000 and 2004. Finally, Shah et al. reported some reverse outcomes among 120 treated patients including fibrosis (24%), hyperpigmentation (20%), radiation skin reactions (7%), as well as accumulation of seroma in breast cavity (7%) considered by some researchers as a natural APBI outcome but not as a complication necessarily,[26] sense of pain in breast (7%), etc.[4] Additionally, other search results and literature reviews showed lack of information about skin reactions in breast cancer patients treated using Intrabeam™ device at least relative to the high dose rate (HDR) therapeutic systems like the MammoSite™ machine, particularly in the Asian countries expectedly due to being newer. In this regard, some complications are often reported in patients treated with Intrabeam™ device including skin complications such as oedema, erythema or accumulation of seroma in treatment cavity, etc.[20] in which the occurrence of any of the outcomes can depend on many individual or demographic characteristics such as breast volume, tumour depth, etc. In this respect, Lee et al.[20] accounted for breast size importance in dose absorption of breast skin in breast cancer patients treated with Intrabeam™ device. Their study demonstrated higher levels of complications among Korean women than those in Iranian individuals mentioned in the present study. It was stated that smaller breast size could lead to less amount of tissue around the applicator and a lower ASD value, which could result in the increased skin absorbed dose. Therefore, the incidence of skin reactions among Iranian women with breasts larger than East Asian women's[27] was less likely; so the results of the present study and those in the investigation conducted in Korea were in agreement in terms of this statement. For this reason, it was argued that small-sized breast patients should be treated

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cautiously. Subsequently, Western women, specially the American ones with larger breasts than Asian women's were expected to be more resistant against potential skin complications after radiation treatment via Intrabeam™ device.[27–29]

Conclusion

The high dose gradient of the Intrabeam™ applicators[9,30] beside the significant uncertainties mentioned made it challenging to achieve a proper dose distribution without any under dose to the target and over dose to the skin. In addition, establishing an optimised ASD (if surgically possible) was in the same way, particularly in shallow treatments. However, most of the authors have recommended at least 1 cm ASD to prevent over dose to the skin.[9,21] Also, implementing the zero depth on the Intrabeam™ TPS as the prescribed depth is preferred rather than 1 cm or 2 cm in order to minimise the dose uncertainties particularly in the first few millimetres of the applicator surface. Overall, due to various treatment parameters of patients including breast size, tumour size, tumour depth and its location in the breast, as well as lack of a reliable TPS, the best possible treatment outcomes with the least probability of skin reactions could be achievable through specialisation of treatment procedures for each patient.

Totally, the observations revealed that breast cancer treatment using the Intrabeam™ device was well tolerated by the patients recruited in the given institute and also the level of skin reaction incidence was acceptable. However, the application of a practical method for skin dosimetry like the TLD measurement or employing radiochromic films such as the EBT2 or the EBT3 would seem more reliable. Actually, a similar project is ongoing in the present institute using the TLDs for in vivo dosimetry in order to obtain an accurate understanding of dose distribution in the target and normal adjacent tissues such as skin, thyroid, contralateral breast and eyes in breast cancer patients who are being treated with the Intrabeam™ device. Since the IORT using the Intrabeam™ device for breast cancer treatment consists of the incidence of less skin reactions compared with using the HDR machines like MammoSite™, it would be preferred for delivering the APBI.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (patients who contributed to this study) and the Declaration of Helsinki (DoH) in 1975, as revised in 2008, and finally approved by Mashhad University of Medical Sciences.

References

1. Njeh C F, Saunders M W, Langton C M. Accelerated partial breast irradiation (APBI): a review of available techniques. Radiat Oncol 2010; 5 (1): 90.
2. Arthur D W, Vicini F A. Accelerated partial breast irradiation as a part of breast conservation therapy. J Clin Oncol 2005; 23 (8): 1726–1735.
3. Vaidya J S. Partial breast irradiation using targeted intraoperative radiotherapy (Targit). Nat Clin Pract Oncol 2007; 4 (7): 384–385.
4. Shah S, Holzwanger E, Khwaja R et al. A single-site retrospective, non-randomized study of accelerated partial breast irradiation brachytherapy for early-stage breast cancer treatment to evaluate local tumor control, cosmetic outcome, and toxicities. Technol Cancer Res Treat 2016; 15 (5): 645–650.
5. Bartelink H, Horiot J-C, Poortmans P M et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. Jo Clin Oncol 2007; 25 (22): 3259–3265.
6. Gunderson L L, Willett C G, Calvo F A, Harrison L B. Intraoperative Irradiation: Techniques and Results. New York: Springer Science & Business Media, 2011: 87–88.
7. Keshtgar M, Pigott K, Wenz F. Targeted Intraoperative Radiotherapy in Oncology. Heidelberg: Springer, 2014.
8. Vaidya J S, Baum M, Tobias J S, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. Eur J Surg Oncol 2002; 28 (4): 447–454.
9. Hensley F W. Present state and issues in IORT Physics. Radiat Oncol 2017; 12 (1): 37.
10. Schneider F, Greineck F, Clausen S et al. Development of a novel method for intraoperative radiotherapy during kyphoplasty for spinal metastases (Kypho-IORT). Int J Radiat Oncol Biol Phys 2011; 81 (4): 1114–1119.
11. Schneider F, Fuchs H, Lorenz F et al. A novel device for intravaginal electronic brachytherapy. Int J Radiat Oncol Biol Phys 2009; 74 (4): 1298–1305.
12. Park C C, Yom S S, Podgorsak M B et al. American Society for Therapeutic Radiology and Oncology (ASTRO) emerging technology committee report on electronic brachytherapy. Int J Radiat Oncol Biol Phys 2010; 76 (4): 963–972.
13. Porock D, Kristjanson L. Skin reactions during radiotherapy for breast cancer: the use and impact of topical agents and dressings. Eur J Cancer Care 1999; 8 (3): 143–153.
14. Warnock C, Lee N. Skin reactions from radiotherapy. Cancer Nurs Pract 2014; 13 (9): 16–22.
15. Kim J, Hill R, Mackonis E C, Kuncic Z. An investigation of backscatter factors for kilovoltage x-rays: a comparison between Monte Carlo simulations and Gafchromic EBT film measurements. Phys Med Biol 2010; 55 (3): 783–797.
16. Shimizu K, Koshida K, Miyati T (eds) Monte Carlo Simulation Analysis of Backscatter Factor for Low-Energy X-Ray. KEK PROCEEDINGS, Kanazawa, 2001: High Energy Accelerator Research Organization; 1999.
17. Ebert MA, Carruthers B. Dosimetric characteristics of a low-kV intraoperative x-ray source: Implications for use in a clinical trial for treatment of low-risk breast cancer. Med Phys 2003; 30 (9): 2424–2431.
18. Eaton D J. Quality assurance and independent dosimetry for an intraoperative x-ray device. Med Phys 2012; 39 (11): 6908–6920.
19. Hubbell J H, Seltzer S M. Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients 1 keV to 20 MeV for elements Z = 1 to 92 and 48 additional substances of dosimetric interest. National Institute of Standards and Technology-PL, Gaithersburg, MD (United States). Ionizing Radiation Div.; 1995.
20. Lee J J B, Choi J, Ahn S G et al. In vivo dosimetry and acute toxicity in breast cancer patients undergoing intraoperative radiotherapy as boost. Radiat Oncol J 2017; 35 (2): 121–128.
21. Eaton D J, Best B, Brew-Graves C et al. In vivo dosimetry for single-fraction targeted intraoperative radiotherapy (TARGIT) for breast cancer. Int J Radiat Oncol Biol Phys 2012; 82 (5): e819–e824.
22. Fogg P, Das K, Kron T, Fox C, Chua B, Hagekyriakou J. Thermoluminescence dosimetry for skin dose assessment during intraoperative radiotherapy for early breast cancer. Australas Phys Eng Sci Med 2010; 33 (2): 211–214.
23. Vicini FA, Beitsch P D, Quiet C A et al. First analysis of patient demographics, technical reproducibility, cosmesis, and early toxicity. Cancer 2005; 104 (6): 1138–1148.
24. Sadeghi A, Prestidge B, Lee J-M, Rosenthal A. Evaluation of the surface radiation dose and dose gradient in early stage breast cancer using high-dose-rate brachytherapy MammoSite™ applicator. Brachytherapy 2006; 5 (4): 230–234.

https://doi.org/10.1017/S1460396918000237 Published online by Cambridge University Press

25. Cuttino L W, Keisch M, Jenrette J M et al. Multi-institutional experience using the MammoSite™ radiation therapy system in the treatment of early-stage breast cancer: 2-year results. Int J Radiat Oncol Biol Phys 2008; 71 (1): 107–114.
26. Patel P S, Yan W, Trichter S et al. Seroma is an expected consequence and not a complication of MammoSite brachytherapy. Breast J 2011; 17 (5): 498–502.
27. Team AHW. AverageHeight.co USA: AverageHeight Website Team; 2017. http://www.averageheight.co/breast-cup-size-by-country. Accessed in November 2017.
28. Anderson J D L, Chandler S C, Mason M A B et al. Scientific analysis reveals major differences in the breast size of women in different countries. J Female Health Sci 2013; 25: 268–292.
29. Average breast size worldwide 2018. https://www.worlddata.info/average-breastsize.php. Accessed in April 2018.
30. Ebert M, Carruthers B, Lanzon P et al. Dosimetry of a low-kV intra-operative X-ray source using basic analytical beam models. Australas Phys Eng Sci Med 2002; 25 (3): 119–123.

https://doi.org/10.1017/S1460396918000237 Published online by Cambridge University Press