
Research Article**Effect of intraoperative radiotherapy on wound healing in breast cancer patient post breast conserving surgery, KSUMC, Riyadh, Saudi Arabia: Case series and review of literature.****Dr. Maha Alamodi Alghamdi^{1,2*}, Abdulaziz Saleh Altwjri³, Abdullah Alsuhaibani⁴, Abdulaziz Alsaif⁵**¹Assistant Professor, King Khalid University, Abha, Saudi Arabia,²Fellow Breast, endocrine surgery, King Saud University, Saudi Arabia.³Fellow Breast -endocrine surgery, King Saud University, Saudi Arabia.⁴King Saud University Medical City,⁵Professor, Breast endocrine surgery, King Saud University, Saudi Arabia

Abstract:

Intraoperative radiotherapy during breast-conserving surgery is being studied as an alternative to 6 weeks of external beam radiotherapy (EBRT) for low-risk women; it can be delivered using electrons (intraoperative electron radiotherapy, IOERT) or 50-kV X-rays. Intraoperative radiation therapy (IORT) may pose a risk for wound complications. Between March 2018 and June 2018, 5 breast cancer patients, all eligible for breast conserving surgery (BCS), were treated at the King Saud Medical city with IORT using the IOERT. Complete data sets for age, stage (T, N, and M), and histology and hormone receptor status were available in 5 cases. Parameters to identify eligible patients are as follows: ESTRO: >50 years, invasive ductal carcinoma/other favourable histology (IDC), T1-2 (≤ 3 cm), N0, any hormone receptor status, M0; ASTRO: ≥ 60 years, IDC, T1, N0, positive estrogen hormone receptor status, M0; TARGIT E “elderly”, risk adapted radiotherapy with IORT followed by external beam radiotherapy in case of risk factors in final histopathology. Consecutive patients operated on with the same surgical technique and given IORT were included. Wound complications were evaluated.

Keywords: Boost, Breast cancer, Electrons, IOERT, Intraoperative radiotherapy, Tumor bed, breast conserving surgery.**Introduction:**

Partial breast irradiation has been established as a suitable treatment option for appropriately selected women with early stage breast cancer by numerous clinical trials dating back to the 1990s. There are several techniques which have been studied to accomplish irradiation of the periphery of the lumpectomy bed as sole therapy after lumpectomy, which is the target volume for any form of partial breast treatment. Intraoperative radiotherapy (IORT) is one such technique [1]. Accelerated Partial Breast Irradiation (APBI) is an approach that treats only the lumpectomy bed plus a 1-2 cm margin, rather than the whole breast. Hence because of the small volume of irradiation, a higher dose can be delivered in a shorter period. There has been growing interest for APBI and various approaches have been developed under phase I-III clinical studies; these include multicatheter interstitial brachytherapy, balloon catheter brachytherapy, conformal external beam radiation therapy and intra-operative radiation therapy (IORT) [1]. The major difference between IORT techniques and other forms of APBI is the timing of the procedure. IORT is most often performed at the time of breast surgery as a single dose, while other APBI technique is performed post-operatively, using target volumes are typically based on CT images and delivering multiple fractions. IORT requires specialized radiotherapy equipment, and there are

several technologies available to provide IORT partial breast irradiation, which deliver treatment with either electrons or 50 kV X-rays [2]. IORT has the advantage of completing the breast-conserving surgery and, in most cases, the partial breast irradiation as one combined procedure. All forms of APBI treat a smaller volume of normal tissue than whole breast radiation (WBRT), thereby reducing the potential lung and cardiac toxicities of radiation treatment, and reducing the overall treatment time compared with whole breast irradiation. IORT has the additional advantage of delivering a single dose at the time of surgery, potentially reduces non-compliance to post-operative radiation, and mastectomy rates among women without ready access to a radiotherapy center [3].

With the expansion of regular screening programs, breast cancer can be detected at an earlier stage in socioeconomically developed countries [4]. Whole breast irradiation (WBI) followed by an additional dose to the tumor bed is accepted as the standard approach in early stage invasive breast cancer treated with breast-conserving surgery (BCS). An alternative to this treatment is partial breast irradiation (PBI), but the effects are not clear. The amount of irradiated breast tissue decreased and treatment time was shortened with PBI in early stage breast cancer. With this technique, normal breast parenchyma and surrounding tissues (e.g., the heart and lungs)

were better preserved, along with better cosmetic results, given local control rates comparable with whole breast radiotherapy [5-8]. Among PBI methods, interstitial brachytherapy, mammocyt techniques, intraoperative radiotherapy (IORT), and three-dimensional conformal/intensity modulated radiation therapy (IMRT) can also be considered [9]. Among PBI techniques, IORT has been the most commonly used and the most popular technique in recent years.

Patient selection is important when recommending IORT, as the final pathology is not available at the time of treatment, so in order to avoid the potential use of subsequent whole breast irradiation, careful pre-operative, and intraoperative assessment can help ensure that high-risk features such as positive margins or positive sentinel nodes are minimized [3]. As all techniques of partial breast irradiation leave some volume of the breast unirradiated, understanding of the selection criteria for each of the various techniques is critical information for clinicians when considering which patients may be appropriately treated with IORT or any other APBI technique. This review will discuss the clinical trial data, patient selection criteria, advantages and disadvantages of partial breast IORT, and published guidelines [3].

Case Series

Case number 1:

56 years old, postmenopausal female patient, known case of HTN, DM, no family history of breast cancer, she had a history of OCP use, multiparous women. She went for breast cancer screening clinic and did mammogram diagnosed as left breast a parenchymal distortion at 2 o'clock position and it is pathologically proven by true cut biopsy (cores of fibrotic breast tissue containing two small foci of invasive and low-grade ductal carcinoma of the breast). Patient evaluated clinically no clear palpable mass on examination. MRI of the breast done and the finding was in correlation with mammogram and breast ultrasound study. The breasts are heterogeneous fibroglandular breast parenchyma with mild asymmetrical background glandular enhancement in left breast likely related to the previous biopsy. Right breast: no suspicious mass or non-mass like enhancement identified, no suspicious right axillary lymph nodes. Left breast: small circumscribed rounded area of low signal intensity in both T1, T2 biopsy site, that representing hematoma which is seen at the area of parenchymal distortion. Adjacent to the hematoma in the 2-3 o'clock position, anterior depth, there are few enhancing foci with no suspicious enhancement, in the upper outer quadrant 2 o'clock position 9 cm from the nipple, there is circumscribed progressively enhancing small mass measuring 0.9x0.6x0.5 cm, no skin thickening or nipple retraction, no chest wall involvement, no suspicious left axillary lymph node involvement.

Histopathology report for the true cut biopsy: Invasive ductal carcinoma, ER-PR positive. The proliferation marker Ki-67 has been done and is positive in 15% of the tumour cells. Wide local excision, SLNB, IOERT. Patient prepared for surgery, hook wire inserted preoperative, wide local excision

done, and the specimen was sent to a mammogram to make sure radiologically from the margin, SLNB was negative for malignancy. Intraoperatively, IOERT gave. Patient seen postoperative no sign of inflammation or infection, discharged in good condition. The patient followed in the clinic for 2 weeks, 1 month, and 3 months post operatively the wound healed with good result.

Case number 2:

57 years old postmenopausal female not known to have any chronic illness, diagnosed as right breast mass discovered incidentally during mammogram screening, no history of a palpable mass, no nipple discharge, no history of skin changes, no history of OCP or hormonal replacement therapy used. Her brother died due to cancer (not known type); her cousin had metastatic breast cancer. On examination: no palpable mass, no skin changes, no nipple retraction, no palpable axillary lymph nodes.

Laboratory and radiological investigations was done. Ultrasound showed right breast 2:00 (2 cm from the nipple) there is an ill-defined heterogeneous hypoechoic vertical oriented mass with posterior shadowing with surrounding parenchymal distortion and it measures 0.7x0.6x0.4 cm. Left breast: 2:00 (5 cm from the nipple) a small sub centimetre avascular cyst. No solid or suspicious masses in the left breast. Bilateral benign axillary lymph node. Impression: right breast highly suspicious mass (BIRAD-5). Mammogram: suspicious mass BIRAD-5. True cut biopsy result showed suggestive of infiltrating mammary carcinoma of the breast (IDC), grade 2 case was discussed. CT scan chest, abdomen, pelvis for staging showed no evidence of malignancy. Bone scan: no evidence of bone metastasis. Treatment plan was hook wire localization, WLE+SLNB+IOERT. Patient was admitted and prepared for the surgery. Right breast ultrasound localization for surgical excision done, images of the mass in the 2 o'clock position were obtained. The breast was prepped for the procedure and the area was anesthetized, using 20 G localization needle and wire and a medial approach, the needle was inserted in to the breast and position of the localizing needle was confirmed under ultrasound guidance, the needle was then exchanged for the localizing wire. Mammogram for the surgical specimen: A single specimen submitted from the OR labelled right breast demonstrates wire and clip associated with mass.

Final Histopathology report: *Specimen A:* right axillary lymph node, paraffin sections confirm the presence of two fatty lymph nodes showing mild reactive changes with no evidence of malignancy and the frozen sections diagnosis was confirmed. *Specimen B:* right breast mass lumpectomy sections show invasive ductal carcinoma of the breast (SBR grade II) with a modified SBR score of 6 (tubules:3, pleomorphism:2, mitosis:1). The tumor maximum diameter is 1.0 cm. A small in situ ductal component of the cibriform and intermediate cell grade is identified. All resections margins are free of carcinoma and there is no evidence of vascular or perineural invasion. The non-neoplastic breast tissue shows foci of fibrosis and several lactiferous ducts. ER: positive

(strong intensity in 70% of tumor cells). PR: positive (strong intensity in 60% of tumor cell). Her-2neu: negative (+1). E-cadherin: positive in tumor cells. Patient came for follow up in outpatient clinic after 2 weeks from surgery doing fine, the wound clean, dry, no sign of inflammation or infection. Case was followed for 2 month, 3 month post operatively and wound was healed.

Case number 3:

55 years old, no family history of breast cancer, diagnosed as early stage left breast cancer clinically and radiologically. Her US and Mammogram result: Bilateral scattered fibroglandular density. There is circumscribed round equal density mass seen at the left outer central aspect measuring 0.7x0.8 cm (8 cm from the nipple) BIRAD4. CT chest, abdomen, pelvis for staging: negative for metastasis; case was discussed and treatment plan was WLE+SLNB+IOERT. Patient prepared for surgery, SLNB confirmed by frozen section is negative for malignancy, the mass excised and sent for the mammogram to make sure that cancer involved. IOERT given, patient seen post operatively doing fine, the wound clean and dry, discharged in good condition. Final histopathology report: Mucinous carcinoma, SBR grade 1 (tubule formation:3, nuclear pleomorphism:1, mitosis:1); Tumor size: 0.9cm; Tumor focality: unifocal. Ductal carcinoma in situ is present, low nuclear grade, cribriform type less than 10%. All margins are free of mucinous carcinoma and DCIS. (The mucinous carcinoma and DCIS are very close to the inferior margin:0.1cm). pTNM staging T1bN0M0; ER: 90% moderate to strong; PR: 60%moderate to strong; Her2-neu: 2+ equivocal; Ki67:15%of cells show nuclear positivity. Patient was decided for close follow up only, no need for external beam radiotherapy. Patient followed in the out patient clinic doing fine, no mass recurrence, wound healed. Patient for close follow up.

Case number 4:

55 years old female with history of wide local excision for benign right breast mass, it was treated 7 years back. She came for annual screening, diagnosed radiologically as left breast suspicious lesion. US, mammogram done for her: Left breast newly seen small 7 mm focal asymmetry in the left upper central aspect about 10 cm from the nipple with somewhat speculated outline measuring 0.3x0.3x0.3 12.00 position, small irregular shadowing hypoechoic mass with surrounding echogenic halo is seen and no intrinsic vascularity on colour Doppler. CT chest, abdomen, pelvis for staging: no evidence of intrathoracic metastasis, no recent distant metastatic lesions seen within abdomen or pelvis. Bone scan done: no evidence of bone involvement. Treatment plan was: HWL+WLE+SLNB+IOERT. Patient was admitted and prepared for surgery.

Intraoperatively SLNB was negative for malignancy, IOERT was given. Post operatively patient was fine, the wound clean, dry, no sign of infection. Discharged on good condition.

Final histopathology report: Specimen A (left axillary sentinel lymph node): negative for malignancy. Specimen B (left

breast) lumpectomy: Microscopic focus of invasive ductal carcinoma (0.3 cm), SBR grade 1 (tumor:1, nuclear:1, mitosis:1). Margins are not involved by carcinoma, negative for lymphovascular invasion. Pathological staging: pT1N0Mx; Immunohistochemistry shows the following result: ER positive strong >90%; PR positive, moderate 80%. Her2-neu: negative; E-cadherin: positive. Patient seen in the clinic post surgery by 2 weeks, 1 month, 2 month. Patient was doing fine, wound was healed.

Case number 5:

65 years old female patient with no past medical or surgical history. All normal vaginal delivery, age of menarche was 12 years old, first pregnancy was at 22 years old, no history of breast feeding, she had history of OCP use for 4 years, she had family history of breast cancer her sister at age of 25, 2 patient cousins at age 40 and 45 years. Patient had huge breast, she came for screening. Mammogram done. Dense breast bilaterally with left breast asymmetrical density and subtle distortion for further evaluation by MRI study BIRAD0. MRI breast: The breasts are heterogeneously dense, there is minimal background parenchymal enhancement. Right breast no suspicious mass or non mass enhancement identified with no suspicious right axillary lymphadenopathy. Left breast: in the approximately 12° clock position, middle to posterior depth (at the fat glandular interface), there is speculated enhancing mass demonstrating mixed kinetic with areas of washout measuring 1.4x1.1x1.1cm, corresponding to the mammographic architectural distortion and is suspicious. No skin thickening or nipple retraction, no chest wall involvement, no suspicious left axillary lymphadenopathy BIRAD-5.

True cut biopsy: Invasive ductal carcinoma, SBR grade1; ERa and PR positive; Ki-67 positive. CT chest, abdomen, pelvis for staging: no evidence of metastasis. Bone scan: no evidence of bone metastasis. Case discussed in the tumor board, the plan was for hook wire localization, wide local excision, SLNB, IOERT. Patient prepared for surgery, intraoperative SLNB was negative for malignancy, IOERT given without immediate complication. Post operative patient doing fine, wound clean, dry, discharged on good condition with follow up.

Final histopathology result: The SLNB confirmed as negative for malignancy. The other specimen (left breast mass, lumpectomy) invasive ductal carcinoma SBR grade 1 (tubular formation 1, nuclear pleomorphism 1, mitosis 1). Tumor measures 0.9cm in maximum dimension, all surgical resection margins are free of carcinoma, no lymphovascular invasion, no perineural invasion. Pathological staging: pT1N0Mx. Patient seen in the clinic post surgery wound healed for adjuvant hormonal, chemotherapy.

Discussion:

Surgical lumpectomy with boost dose to the periphery has shown to decrease the risk of local recurrence in younger women, patients with higher grade and those with positive margins or extensive lymphovascular invasion (10). Highest density of residual microscopic cells were present in tissues in

close proximity to primary cancer and this has highest risk for local recurrence. Many studies have followed using IORT as a boost with planned WBRT. The importance of using IORT as boost include when boosting a CT-based volume, the capability to visualize directly the tumor bed and thereby prevent marginal misses. The same BED, oxygenation, and biological advantages theoretically present for single dose IORT may be relevant for IORT boost as well, and are under investigation. Using either IOERT (intraoperative electrons) or 50 kV IORT were used in several studies as a boost have been reported. Ongoing studies going IORT boost include the TARGIT-Boost (11) and HIOP trials (12).

International Society of Intraoperative Radiotherapy has been reported IOERT boost as a pooled analysis (34). In this analysis, 1,109 unselected patients from seven European centers, 60% of whom had at least one high risk factor, were treated similarly with IOERT boost at a median dose of 10 Gy and a subsequent whole breast dose of 50–54 Gy. After a median follow-up of 5 years, the local recurrence risk was 0.8%, half seen in the index quadrant. Risk factors for recurrence included high grade, age under 40, and ER negative. Upon examining the impact of delays from IOERT boost to WBRT, no impact on local recurrence of delays up to 140 days was seen. The Salzburg IOERT group conducted a matched-pair analysis of IOERT boost and external electron boost patients, who had IBR rates at 10 years of 1.6 and 7.2%, respectively (13). Low-energy X-rays IORT as a boost has been reported in two cohort series. One multicenter pilot study treated with 20 Gy to cavity surface intraoperatively followed by 45–50 Gy whole breast in 299 women undergoing lumpectomy. After a median follow-up of 5 years, the observed local recurrence rate was 2.7% (14). A single institution series of 197 patients received an IORT boost of 18–20 Gy then 46–50 Gy whole breast, reporting a 5-year local relapse free survival of 97% (15).

Adjuvant radiotherapy after BCS in early-stage breast cancer is extremely important. When IORT was applied directly to the tumor bed during surgery, the skin and subcutaneous tissue were removed from the radiation field to decrease radiation dose, so that the duration of treatment was shortened. BCS and external beam radiotherapy (EBRT), along with an additional dose to the tumor bed, are standard for treatment of early-stage breast cancer. In the literature, IORT is a relatively new technique for wound complications compared with EBRT. Therefore, the adverse effects were assessed both for late skin toxicity and cosmetic results. In one study, 1119 patients had been randomized to the external beam radiotherapy arm and 1113 patients to the IORT arm. Rates of hematoma, seroma, wound dehiscence, and wound infection in the IORT group were 1%, 2.1%, 2.8%, and 1.8%, respectively. Rates in the EBRT group were 0.6%, 0.8%, 1.9%, and 1.3%. Only seroma was found to be higher in the IORT group, with a statistically significant difference (16). Ruano-Raviana et al. reviewed 15 studies by comparing the reliability of IORT and EBRT. In their review, the most common wound complication, after fibrosis and skin reactions, in the IORT group was seroma. These complications were much higher for patients in the

EBRT group, although rates ranged from 3% to 25% (17). The number of patients in studies focusing on early wound problems is relatively small. In a study comprising 55 patients, focusing on early complications of IORT from Australia, the description was similar to that of our own study, with seroma being reported in 51% of the patients (18). In an IORT study with 72 patients from China, the average time for complete healing of a BCS incision was 13–22 days in the IORT arm and 9–14 days in the EBRT arm (19). In other in vitro studies, changes in the microenvironment caused by IORT in the surgical field were found to inhibit the activation of hormonal pathways necessary for wound healing: cytokines specifically, as well as epidermal growth factor, could not be activated (20).

When considering use of IOERT techniques for partial breast treatment after lumpectomy, it is recommended to select patients who fall into the low-risk categories among published guidelines, using the “suitable” or “good risk” criteria for patients who are general candidates for APBI. IOERT has potential advantages over external or brachytherapy-based techniques given the direct visualization of and contact with the target tissue and the immediacy of treatment, but has the disadvantage of lacking final pathologic assessment of the margins and sentinel nodes, placing a percentage of women at risk of being recommended to undergo additional external beam irradiation.

To discuss the specific factors affecting wound complication in our case series. Factors such as advanced age, obesity, diabetes, hypertension, anemia, COPD, weight of the specimen, and smoking have been proposed to affect wound complication in breast cancer surgery, which includes aspects of surgical procedures in other studies (21). We conclude that IORT might have a negative effect on seroma formation, SSI, and healing time. It should be kept in mind, however, that in centers with IORT implementation, the complication rate might also increase. Necessary measures for better sterilization in the operating room should be taken, while patient wound healing should be monitored closely. It is clear that the adverse effects of IORT on wound complications should be closely watched.



Fig 1: Intraoperative Preparation For IOERT

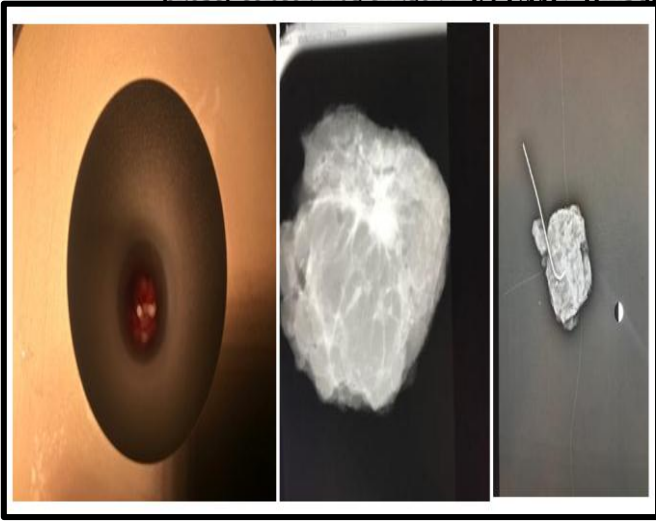


Fig 2: Post excision of mammographic images

Conclusion:

Breast IOERT is currently primarily a technique for partial breast irradiation which has been well established as an option for patients who are otherwise appropriate candidates for APBI. When intended to be used for partial breast treatment, patient selection should focus on clinicopathologic factors predictive of negative nodes and negative margins. Careful assessment of pre-operative mammographic and other imaging studies for features, such as extent of calcifications, may be helpful. Intraoperative techniques can be useful as well, including assessment of margins and sentinel nodes intraoperatively, and careful excision technique to maximize clear margins, such as taking additional shave margins as needed.

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