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Intraoperative boost radiation effects on early wound complications in breast cancer patients undergoing breast-conserving surgery

Mehmet Ali GÜLÇELİK, Lütfi DOĞAN*, Niyazi KARAMAN, Müjdat TURAN, Yavuz Selim KAHRAMAN, Gökhan Giray AKGÜL, Cihangir ÖZASLAN
Department of Surgery, Oncology Hospital, Ankara, Turkey

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Background/aim: Intraoperative radiation therapy (IORT) may pose a risk for wound complications. All technical aspects of IORT regarding early wound complications were evaluated.

Materials and methods: Ninety-three consecutive patients operated on with the same surgical technique and given (study group) or not given (control group) IORT were included. Wound complications were evaluated in two groups.

Results: Forty-three patients were treated with boost dose IORT and 50 patients were treated with breast-conserving surgery without IORT. When both groups were compared in terms of early postoperative complications, there were 11 (25.5%) patients with seroma in the IORT group and 3 patients (6%) in the control group (P = 0.04). While 9 (21%) patients were seen to have surgical site infection (SSI) in the IORT group, there was 1 (2%) SSI in the control group (P = 0.005). There were 15 (35%) patients with delayed wound healing in the IORT group and 4 patients (8%) in the control group (P = 0.006).

Conclusion: IORT could have a negative effect on seroma formation, SSI, and delayed healing. It should be kept in mind, however, that in centers with IORT implementation, the complication rate could also increase. Necessary measures for better sterilization in the operating room should be taken, while patient wound healing should be monitored closely.

Key words: Breast cancer, intraoperative radiotherapy, wound complications

1. Introduction

With the expansion of regular screening programs, breast cancer can be detected at an earlier stage in socioeconomically developed countries (1). 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 (2–5). Among PBI methods, interstitial brachytherapy, mammocyte techniques, intraoperative radiotherapy (IORT), and three-dimensional conformal/intensity modulated radiation therapy (IMRT) can also be considered (6). Among PBI techniques, IORT has been the most commonly used and the most popular technique in recent years.

In IORT, the tumor bed is irradiated under direct observation during the operation and completed by a single application with lower doses to surrounding tissue. In WBI, patients must come to the hospital on a daily basis for 6–7 weeks. When PBI is conducted with IORT techniques, treatment time is shortened from 6–7 weeks, and local treatment is completed with a single application in well-chosen cases. Thus, patients are offered an acceptable and easier treatment process in terms of their social lives. As a result, the cost of treatment is reduced, with skin toxicity reduced to a minimum as well, along with better cosmetic results (7,8).

From the surgeon's view point, this is a new situation that should be clarified. An open wound is manipulated, while radiation is delivered in this relatively new technique; however, this may pose a risk for infective wound complications. In this study, all technical aspects of IORT regarding early wound complications were evaluated.

* Correspondence: lutfidogan1@yahoo.com

2. Materials and methods

Ninety-three consecutive patients treated with the same surgical technique (conventional level I BCS, with up to 20% removal of breast volume and intraglandular flap mobilization), either given (the study group) or not given (the control group) IORT between November 2013 and December 2014 were evaluated retrospectively. Patients in the study and control groups were given 45–50 Gy WBI following adjuvant systemic treatments. As the purpose of this study was to investigate the effects of IORT, complications in the early period (postoperative first 1 month) were recorded before WBI.

The patients with reexcision or mastectomy due to positive surgical margins with early follow-up in other centers, versus those who underwent BCS after neoadjuvant therapy were excluded. Inclusion of patients in the IORT program was decided on by a panel of experts in medical oncology, radiation oncology, surgical oncology, pathology, radiology, and anesthesiology. Lymphoscintigraphy with radiocolloid material was performed before surgery for sentinel lymph node biopsy. Direct axillary dissection was carried out in patients with clinically positive axilla.

Patients in the study group with the highest risk of local recurrence were administered a boost dose of IORT to the tumor bed, using a mobile Mobetron (Intraop Medical Incorporated, Santa Clara, CA, USA) in the operating room. Intraglandular flaps were prepared to allow for the placement of acrylic discs and were sutured temporarily after acrylic disc placement under the flaps. IORT with a total boost dose of 10 Gy was applied after the placement of the appropriate applicator as shown in the Figure. After completion, the acrylic disc was removed by release of temporary flap closures, while glandular flaps were sutured to one another and the muscles. The excision field in all control group patients was covered with intraglandular flaps. All patients underwent SLNB and if the SLNB was negative, no additional intervention to the axilla was performed. Level 1–2 axillary dissection was performed for all SLNB-positive patients. A closed suction drain was placed in the lumpectomy area, while the axillary area was drained in all patients with axillary node dissection.

Age, radiologic tumor size, pathologic tumor size, actual tumor size, the distance to skin and pectoral muscle, flap thickness, hormone receptors and cerbB2 status, hypertension, diabetes, comorbidities such as heart and lung disease, and smoking (packs/year) were recorded. Wound complications were evaluated in two groups, as having minor or major complications. Seroma, hematoma, surgical site infection (SSI), delayed wound healing, and incisional wound dehiscence were evaluated in the minor group. Major serious complications such as incisional wound dehiscence were evaluated in the major group. Serous fluid collection, creating patient discomfort and tension, led to both incision and drainage; they were considered as seroma. Conversely, collections that caused hemorrhagic bruises on the skin were considered to be hematomas. Erythema, purulent discharge, localized temperature increases, cellulitis, pain, redness, and tenderness (whether confirmed with wound culture or not) were considered to be SSI. Simple incision dehiscence repaired by simple suturing was classified as minor, while repair of the whole incision in an operating theater was classified as major wound dehiscence. Wound dehiscence that heals without intervention was regarded as late-wound healing.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The differences between the groups were analyzed with the Mann–Whitney U test, and the chi-square test was carried out for the comparison of the complications. P values less than 0.05 were accepted as statistically significant.

3. Results

The study included 93 early-stage breast cancer patients, with 43 treated with boost dose IORT and 50 patients treated with BCS without IORT. Twenty-one patients were given IORT in the first year of the study (early group) and 22 patients in the second year (late group). Despite

Figure. Acrylic disc placement under the flaps and application of 10 Gy boost dose.

the time needed for intraoperative preparation for IORT in the early group, which took 33 min, this was decreased to 17 min in the late group. The average time for IORT application was 2 min. The median age of patients in the study was 53 (48–67) years. While the median size of the tumors at radiological examination was 17 (11–27) mm, it was 20 (12–27) mm at pathological examination. The average distance of tumors to the skin, areola, and pectoralis major muscle was measured as 2 cm, 4 cm, and 2 cm, respectively. While the average skin flap thickness was 1.6 cm, the average specimen weight was 266 ± 83 g. Estrogen receptor (ER) and progesterone receptor (PR) positivity were confirmed in 79 and 27 patients, respectively, while cerbB2 was negative in 69 patients. The grade distribution of patients from grades 1 to 3 was 18, 47, and 28 patients, respectively. The tumor characteristics of the two groups are shown in Table 1. When the study and control groups were compared, there were no significant differences in age, radiologic tumor size, pathologic tumor size, distance of tumor to the skin, areola, and pectoral muscle, flap thickness, weight of the resected specimen, and tumor characteristics, such as hormone receptors, grade, and cerbB2.

When both groups were compared for early postoperative complications; there were 11 (25.5%) patients with seroma in the IORT group and 3 patients (6%) in the control group (P = 0.04). While 9 (21%) patients had SSI in the IORT group, there was 1 (2%) with a SSI in the control group (P = 0.005). There were 15 (35%) patients with delayed wound healing in the IORT group and 4 patients (8%) in the control group (P = 0.006). While 1 patient had a hematoma in the control group, there were none in the IORT group. Additionally, while 3 (7%) patients had minor wound dehiscence in the IORT group, there was no wound dehiscence in the control group. There was no statistically significant difference between the groups with respect to hematoma or minor wound dehiscence, with no major wound dehiscence in either group (Table 2).

Eleven (25.5%) patients in the study group and 15 (30%) patients in the control group had undergone axillary dissection. There were 3 patients with diabetes, 9 patients with hypertension, and 2 patients with COPD in the study group, while there were 2 patients with diabetes and 10 patients with hypertension in the control group. There were no smokers in either group. Axillary dissection, patient and tumor characteristics, and comorbidities had

Table 1. General characteristics of patients.

		IORT (n: 43)	Control group (n: 50)	P value
Age		51.6 ± 11.8	49.6 ± 10.4	0.4
Radiological tumor size		17.3 ± 5.2	19.06 ± 6.2	0.2
Pathological tumor size		20.3 ± 7.5	22.5 ± 8.4	0.1
Tm distance to pectoral muscle		23.5 ± 7.6	25.7 ± 8.7	0.4
Tm distance to areola		34.2 ± 9.2	40.3 ± 6.9	0.4
Tm distance to skin		20.9 ± 6.6	27.8 ± 9.1	0.3
Flap thickness		15.7 ± 5.1	15.8 ± 0.8	0.1
Length of incision		11.9 ± 2.3	12.1 ± 1.9	0.09
Specimen weight		266.1 ± 93.1	235.5 ± 52.5	0.4
Er	(–)	6 (14%)	8 (16%)	0.4
	(+)	37 (86%)	42 (84%)	
Pr	(–)	12 (28%)	16 (32%)	0.2
	(+)	31 (72%)	34 (68%)	
Cerbb2	(–)	33 (77%)	36 (72%)	0.3
	(+)	10 (23%)	14 (28%)	
Grade	I	8 (18.5%)	10 (20%)	0.1
	II	21 (49%)	26 (52%)	
	III	14 (32.5%)	14 (28%)	
Axillary dissection	(+)	11 (25.5%)	15 (30%)	0.2
	(–)	32 (74.5%)	35 (70%)	

Table 2. Postoperative complications.

		IORT (n: 43) %		Control group (n: 50) %		P value
Seroma	(+)	11	25.5	3	6	0.04
	(–)	32	74.5	47	94	
SSI	(+)	9	21	1	2	0.005
	(–)	34	79	49	98	
Hematoma	(+)	0	0	1	2	0.2
	(–)	43	100	49	98	
Minor dehiscence	(+)	3	7	0	0	0.09
	(–)	40	93	50	100	
DWH	(+)	15	35	4	8	0.006
	(–)	28	65	46	92	
Major dehiscence	(+)	0	0	0	0	0.5
	(–)	43	100	50	100	

SSI: Surgical site infection, DWH: Delayed wound healing

no effect on early wound complications. IORT was the only significant factor on seroma formation (P = 0.03), SSI (P = 0.02), and delayed wound healing (P = 0.02). Seven of the 11 patients with a seroma (63%), 7 of the 9 patients with SSI (78%), and 10 of the 15 patients with delayed wound healing in the study group (67%) had had surgery in the first year of the study period.

4. Discussion

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. However, our study focused on early postoperative problems. The TARGIT study was a prospective, randomized, noninferiority assessment released in 2010, with patients under 45 who were undergoing BCS in 28 centers. In that 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 (2). In that study, bleeding that required surgical exploration was considered as hematoma, while collections that required antibiotics and surgical drainage were defined as wound infections. Low rates of wound complications in that study might also be associated with their description. 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% (9).

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 (10). 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 (11).

In studies investigating the in vitro effects of IORT, changes in the cellular phenotype of the surgical wound and wound fluid, including a change in tissue composition that weakened the physical connection between cells, had been expressed. This issue between cells prevents the introduction of intracellular signaling pathways, to help initiate wound healing. The novel microenvironment is considered to be nonideal for the invasion of tumor cells (12). 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 (13). The new microenvironment is not suitable for migration of cells, which prevents the invasion of possible residual tumor cells in the surgical field (14). Keratinocyte migration to the surgical field is required for the epithelialization phase of wound healing. The production of a new connective tissue matrix also begins with fibroblast migration. The distribution of cell migration could similarly disrupt these phases of wound healing. Radiobiologically, it was known that the administration of high-dose radiation to a limited area could lead to vascular damage. The most important factors adversely affecting wound healing in surgical practice are reduction of blood flow and hypoxia. This might explain the high wound complication rate in patients undergoing IORT.

To discuss the specific factors affecting wound complication in our series, the time spent in preparation of IORT should be added to both total operation time and prolonged operation time, each of which could be a factor. In the present study, which reflects our first experience with patients treated with IORT, 33 min was added in the first year of the study and it was a striking feature. Apart from this, next to the surgical team, radiation oncologists, technicians, and physical engineers were included in the operating room, creating an unusually crowded room. Another factor might be the possible violation of sterility rules in the facilitation of the IORT device at the operating table. As the experience of the team increased with higher numbers of procedures, operations in the second year were only prolonged by an average of 17 min. Moreover, as the number of procedures increased, the number of people in the operating room became more restricted and sterility rules were complied with more easily. It is remarkable that the critical part of wound complications occurred in the first year of the study.

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 (15). In our study, comorbidities of patients did not affect the complication rate. A possible explanation was thought to be the small number of patients with comorbid diseases in each group. Likewise, our series did not have any patients with a smoking history.

In recent years, IORT as a method for the local treatment of breast cancer is being used at an increasing rate. Our hospital is one of the first centers in the country using this technique. As a result, its impact on local recurrence rates and wound healing is important for surgeons. This study reflects our early experience with IORT. We conclude that IORT might have a negative effect on seroma formation, SSI, and healing time. As our experience increases, these adverse effects of IORT might also decrease. Further studies with increased numbers of patients are needed from centers in which IORT has been used for longer periods. 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.

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