

Complication analysis of breast cancer patients after mastectomy with immediate autologous breast reconstruction and adjuvant radiotherapy

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ABSTRACT

Background: After the mastectomy, the complication is different depending on the sequence and method of breast reconstruction and Radiotherapy (RT). The aim of the current study was to investigate complication rates, related factors, and time to complications in breast cancer patients who underwent mastectomy with immediate autologous breast reconstruction (IABR) and adjuvant RT. **Materials and Methods:** Between April 2009 and January 2017, 52 patients underwent mastectomy with IABR followed by RT. Medical records of patients were retrospectively reviewed. Complications occurring after RT initiation were evaluated in four aspects: fat necrosis, wound infection, revision surgery, and re-reconstruction and classified into: 1) minor complication requiring only conservative treatment, and 2) major complication requiring surgical correction. All patients received RT on the chest wall including total flap. Ipsilateral axillary, supraclavicular and internal mammary regions were included at physician's discretion. Median RT dose was 50.4 Gy (range, 50.4 – 59.4 Gy). **Results:** Median follow up duration was 22.3 months (range, 5.3-98.6 months). Complication after RT initiation occurred in 9 (17.3%) patients. Six (11.5%) patients showed minor complications. Three (5.8%) patients developed major complications. Median time to occurrence of complication after RT was 8.6 months (range, 1.8–25.1 months). Two-thirds of complications occurred within one year, while 88.9% occurred within two years after RT. No factor showed correlation with complication. **Conclusions:** IABR followed by adjuvant RT may be a reasonable option for patients who underwent mastectomy, in terms of postoperative complication. Complications occur most frequently within 1 year after initiation of RT, and most occur within 2 years.

Keywords: Radiotherapy, breast reconstruction, mastectomy, complication.

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INTRODUCTION

For patients who have undergone mastectomy, breast reconstruction is an important procedure as it increases psychosocial satisfaction⁽¹⁻⁴⁾. However, patients scheduled for post-mastectomy radiotherapy (PMRT) are

concerned about postoperative complications and cosmetic degradation due to radiotherapy (RT). To maintain the cosmetic result while minimizing complications, several studies have been conducted to determine optimal timing and technique of breast reconstruction in patients with adjuvant RT⁽⁵⁻¹⁰⁾. Although no clear

consensus has been reached. Immediate breast reconstruction (IBR) has advantages including a single operation, shorter postoperative recovery period, superior cosmetic results, and more psychosocial benefit compared to delayed breast reconstruction (3, 4, 11, 12). In addition, recent studies have shown that immediate autologous breast reconstruction (IABR) followed by RT does not increase complication rate compared to delayed reconstruction (8-10, 13, 14). However, previous studies included some patients using tissue expander or autologous and prosthetic implants together (15-19). In addition, factors related to complications were analyzed mainly according to surgical methods and patient factors other than RT factor (20-22). The aim of the present study was to evaluate complication rates and time to complication after adjuvant RT in patients who had undergone pure IABR, excluding patients who using tissue expander or autologous tissue and prosthetic implant together. We also investigated the correlation between a wider range of factors, including RT factors and complication.

MATERIALS AND METHODS

MATERIALS AND METHODS

Medical records of the 52 patients who received mastectomy with IABR followed by adjuvant RT between April 2009 and January 2017 were retrospectively reviewed. All complications that occurred from after IABR date were investigated and assessed through a review of patient's medical records. Complications occurring after RT initiation were evaluated in four aspects: fat necrosis, wound infection, revision surgery and re-reconstruction. Fat necrosis was evaluated either clinically by patient's symptoms, physician's palpation, and ultrasound or pathologically through tissue obtained from any surgical intervention including delayed nipple areolar complex (NAC) reconstruction. Wound infection was defined as the presence of symptoms such as pain, heat, edema, erythema in wound site, and the need for antibiotic treatment. Revision surgery was defined as any

surgical intervention performed to solve a wide range of necrosis, wound dehiscence or wound infection. Re-reconstruction was defined as re-performing the breast reconstruction for any reason after IABR. Based on these criteria, minor complication was defined as cases that received conservative treatment because of mild symptoms and limited range of complications. And, major complication was defined as cases needed revision surgery or re-reconstruction. We also evaluated factors such as body mass index (BMI), flap size (g), flap kindness, interval between adjuvant RT and IABR, RT field, chest wall clinical target volume (CTV), and dose homogeneity index (DHI) that might be associated with complication. Flap size (g) was evaluated by final flap weight used for breast reconstruction, according to the surgical record, excluding the part removed from trimming and de-epithelization of initial harvest flap. The chest wall CTV was delineated according to RTOG definitions (23). The clinical stage of the patient was investigated at the time of diagnosis according to the American Joint Committee on Cancer (AJCC) staging, 8th edition. DHI was estimated for clinical target volume (CTV) of the chest wall. It was calculated using equation 1.

$$DHI = \frac{D5}{D95} \quad (1)$$

Surgery

Mastectomy was performed in three ways: simple mastectomy, modified radical mastectomy (MRM), and nipple areolar complex (NAC) preserving MRM. Breast reconstruction was performed consecutively after mastectomy for all patients, using three flap types as follows: free transverse rectus abdominis muscle (TRAM) flap, pedicled latissimus dorsi musculocutaneous (pedicled LD MC) flap, and free deep inferior epigastric perforator (DIEP) flap. Breast reconstruction was performed by two plastic surgeons following the same procedure.

Radiotherapy

Simulation computed tomography (CT) was performed using a Somatom Sensation Open helical scanner (Siemens Medical Solutions,

Erlangen, Germany) with 3 mm thickness. For simulation, all patients used a vac-lock immobilization device with a 10 degree tilted breast board. RT was delivered on the ipsilateral chest wall including total flap to all patients. Some patients were irradiated for axilla level I-III, supraclavicular (SCV), or internal mammary region according to the physician's discretion. The chest wall irradiation was conducted with 6- or 10- MV photon beams of two tangential fields that covered chest wall and axillary level I. SCV field was treated with 6- or 10-MV photon beams with a posterior axillary boost field to cover the axillary level II-II and SCV regions. Tangential field and SCV fields were placed using the monoisocentric technique: Tangential field and SCV fields are half-beam blocked using same isocenter. For internal mammary node irradiation, 6 MeV electron boost field was used. In all radiotherapy planning, the Pinnacle planning system (Philips Healthcare, Fitchburg, WI, USA) was used. All patients were treated using Siemens ARTISTE linear accelerators (Siemens Medical Solutions, Erlangen, Germany). All patients were irradiated with 1.8 Gy of fraction size, up to 50.4 Gy. Electron boost RT (8-12 MeV) was performed on the surgical scar for cases with a close resection margin of less than 2 mm. At least 90% of the prescription dose covered the target.

Follow-up, study endpoints and statistical analysis

Patients underwent follow-up by a surgeon and a radiation oncologist after surgery and radiotherapy at 3-months intervals for 1 year, 6-months intervals for up to 1-5 years, and 1-year interval thereafter. During follow-up, history taking and physical examination were performed. Breast mammography and ultrasound were performed at 6-months intervals until 5 years, and 1-year interval thereafter.

The primary endpoint of this study was occurrence of complication. Follow-up period was defined as the time from the date of RT initiation until the date of the last visit. Complication free survival (CFS) was defined as the time from the date of RT initiation until the

date of occurrence of any complication. Actuarial two-year CFS was analyzed by the Kaplan-Meier method. Statistical significance between prognostic factor and CFS were assessed using the log-rank test. A p value less than 0.05 was defined as statistically significant. All statistical analyses were performed using SPSS version 21 (IBM, Chicago, IL, USA).

RESULTS

Patient characteristics and treatment characteristics

A total of 52 stage IIA-IIIC breast cancer patients who underwent mastectomy with IABR followed by adjuvant RT were analyzed. Their median follow-up duration was 22.3 months (range, 5.3 – 98.6 months). Median age was 44 years (range, 24 – 65 years). There were two diabetic patients. Obese patients (BMI>30) were two. These patients' characteristics are summarized in table 1.

The majority of patients (45, 86.6%) underwent modified radical mastectomy (MRM). Simple mastectomy was performed in 6 patients, and nipple areolar complex (NAC) preserving MRM in 1 patient. Delayed NAC reconstruction was performed in 23 patients (44.2%) with a median interval of 10.5 months (range, 5.3 – 42.6 months) from immediate breast reconstruction. In Breast reconstruction, free TRAM flap, pedicled LD MC flap, and free DIEP flap were used in 11, 9, and 32 patients, respectively. DIEP flap was the main type (81%) of breast reconstruction. The median flap size (g) used for breast reconstruction was 1538.6 g (range, 152 – 2612.5 g). All patients underwent chemotherapy. Neo-adjuvant chemotherapy was performed in 4 patients, adjuvant chemotherapy in 30 patients, and 18 patients underwent both neo-adjuvant chemotherapy and adjuvant chemotherapy. The majority (90.4%) of patients received radiotherapy up to 50.4 Gy / 28 fractions. Boost RT with 9 Gy / 5 fractions was performed for 3 patients (5.8%) with close resection margin. Four patients were irradiated on chest wall only, 46 patients on chest wall, axilla, and SCL, and 2 patients were irradiated

including IMN. 0.5 cm bolus used in one patient. The median interval between IABR and adjuvant RT was 5.7 months (range, 0.7–9.6 months). The median chest wall CTV was 687 cm³ (range, 226 – 2359 cm³). DHI was measured based on prescription dose up to 50.4 Gy, excluding three patients who received boost RT. Median DHI was 1.4 (range, 1.0–2.3).

Complication occurrence

After breast reconstruction, complication occurred in 15 patients (28.8%). Of these, seven patients (13.4%) developed complication before RT and underwent surgical intervention due to flap failure, venous insufficiency or wound problem. One patient showed venous insufficiency and wound dehiscence either. These complications and interventions prior to RT are summarized in table 2. After RT initiation, complications occurred in 9 (17.3%) patients, one of which had already shown complications before RT. Six (11.5%) patients showed mild fat necrosis, which, as it produced mild symptoms and a limited range of lesion, received conservative treatment only. Wound infection did not occur in any patient. Three (5.8%) patients had major complications requiring surgical intervention. One of them had sustained wound dehiscence before RT, so she

underwent debridement and local flap coverage 3 months after RT complement, and finally received re-reconstruction using a prosthetic implant due to breast asymmetry. The other patient received re-reconstruction using prosthetic implant due to fat necrosis near the nipple, which was about 1/4 of total breast. Finally, the other patient received revision surgery to remove necrotic tissue, and Limberg local flap coverage. Complication occurrence after RT initiation is summarized in table 3.

The median time to occurrence of complication from RT initiation was 8.6 months (range, 1.8 - 25.1 months). Two-thirds of these complications occurred within one year while 88.9% occurred within two years of RT initiation (figure 1).

Patient's and treatment factors that might be associated of complication were analyzed. Age, flap size (g), chest wall CTV (cm³), and DHI were divided into two groups based on the median value of patients. However, none of them showed any significant correlation with two-year CFS. Large flap size (> 1538.6 g) did not show significant correlation with 2- year CFS (92.9% vs. 75.7%, $p = 0.159$). Longer interval (> 6 months) between IABR and RT, Chest wall CTV (cm³), boost RT, RT field, and higher DHI (>1.4) had no significant correlation either (table 4).

Table 1. Clinical characteristics of patients.

Characteristics	No. of patients (%)
Age (years)	
Median, 44 (range, 24-65)	
< 44	25 (48.1%)
≥ 44	27 (51.9%)
AJCC stage	
IIA	4 (7.7%)
IIB	14 (26.9%)
IIIA	24 (46.1%)
IIIB	3 (5.8%)
IIIC	7 (13.5%)
DM	
(+)	2 (38.4%)
(-)	50 (96.2%)
BMI	
Median, 23 (range, 17.0 – 32.9)	
< 30	50 (96.2%)
≥ 30	2 (3.8%)

Abbreviations: No., number; AJCC, American Joint Committee on Cancer; DM, diabetes mellitus; BMI, body mass index.

Table 2. Postoperative complications and surgical intervention before radiotherapy.

Complication	No. (%)	Surgical intervention
Graft failure	2 (3.8%)	Revision surgery
Flap congestion	1 (1.9%)	Flap revision
Venous insufficiency	3 (5.8%)	Flap removal & local flap coverage: 2 (3.8%)
		Re-anastomosis of vessel: 1 (1.9%)
Wound infection	1 (1.9%)	Debridement & secondary closure
Wound dehiscence	1 (1.9%)	Debridement & secondary closure

Abbreviations: No., number

Table 3. Occurrence of complication after RT initiation.

	Total complication	*Minor complication	†Major complication	
			N (%)	Intervention
No. (%)	9 (17.3%)	6 (11.5%)	3 (5.8%)	Revision surgery: 1 (1.9%) Re-reconstruction: 2 (3.9%)

Abbreviations: No., number

*Minor complication, defined as case receiving conservative treatment only.

†Major complication, defined as case requiring surgical intervention.

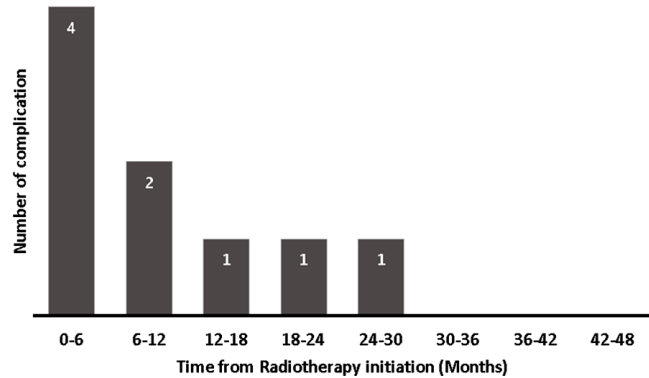


Figure 1. Time of occurrence of complication. Assessment of incidence of complication according to time after RT initiation. Complication occurred in 9 (17.3%) patients during the follow up period. Six complications (66%) occurred within one year, and most complication (8, 88.9%) occurred within two years of RT initiation. After 26 months, no complication occurred.

Table 4. Univariate analysis for occurrence of complication.

Factor		No (%)	2-year CFS (%)	P-value
Patient's factor				
Age(years)	< 44	25 (48.1%)	86.4	0.371
	≥ 44	27 (51.9%)	76.4	
DM	(+)	2 (3.8%)	83.9	0.6
	(-)	50 (96.2%)	68.6	
BMI	< 30	50 (96.2%)	80	0.5
	≥ 30	2 (3.8%)	100	
Surgery				
Mastectomy	Simple mastectomy	6 (11.5%)	80	0.9
	MRM	45 (86.6%)	80.2	
	NAC preserving MRM	1 (1.9%)	-	
Reconstruction type	Free TRAM flap	11 (21.2%)	72.7	0.489
	Pedicled LD MC flap	9 (17.3%)	85.7	
	Free DIEP flap	32 (61.5%)	81.0	
Flap size (g)	≤ 1538.6	22	92.9	0.159
	> 1538.6	22	75.7	
Chemotherapy				
Chemotherapy timing	Neo-adjuvant	4 (7.7%)	75	0.748
	Adjuvant	12 (23.1%)	81.3	
	Neo-adjuvant & adjuvant	18 (34.6%)	81	
Radiotherapy				
Field	Chestwall	4 (7.7%)	75	0.1
	Chestwall, axilla& SCV	46 (92.3%)	82.4	
	Chestwall, axilla, SCV & IMN	2 (3.8%)	-	
Boost RT	Yes	3 (5.8%)	79.2	0.352
	No	49 (94.2%)	100	
Bolus	Yes	1 (1.9%)	80.3	0.6
	No	51 (98.1%)	100	
Interval between IABR and RT	≤ 6 months	27 (51.9%)	83.9	0.805
	> 6 months	25 (48.1%)	78.1	
Chestwall CTV (cm ³)	≤ 687 cc	26 (50%)	81.6	0.8
	> 687 cc	26 (50%)	79.5	
DHI	≤ 1.4	35	84.4	0.223
	> 1.4	17	74.1	

Abbreviations: No, number; CFS, complication-free survival; DM, diabetes mellitus; BMI, body mass index; MRM, modified radical mastectomy; NAC, nipple areolar complex; TRAM, transverse rectus abdominis muscle; Pedicled LD MC, pedicled latissimus dorsi musculocutaneous; DIEP, deep inferior epigastric perforator; IABR, immediate autologous breast reconstruction; SCV, supraclavicular; IMN, internal mammary node; RT, radiotherapy; CTV, clinical target volume; DHI, dose homogeneity index.

DISCUSSION

The purpose of this study was to investigate complication rate, related factors and time of occurrence of complication in patients who underwent IABR followed by adjuvant RT. We found that total complication after breast reconstruction occurred in 15 patients (28.8%), in 9 (17.3%) of them after initiation of RT. Major complications requiring surgical intervention occurred in 9 patients (17.3%) after breast reconstruction, in 3 (5.8%) of them after RT initiation. Although with some variation in the complication rate of each study, this result was similar to another study that analyzed complications of patients who underwent IABR and adjuvant RT (table 5). In contrast, studies analyzing patients who underwent mastectomy with IABR but without RT, reported from 26.9% to 52.4% total complications after reconstruction and fat necrosis from 10.5% to 24.4% (13, 25, 26). In the study by Berry et al, total complication was 32.5% and major complication, requiring surgical intervention, was 20.5% in patients who underwent IABR without RT (26). Since our study showed similar or lower levels of complications than studies of postoperative complication of IABR without RT, IABR with adjuvant RT may be acceptable in terms of postoperative morbidity.

Also, we analyzed the time to complication after initiation of RT. About two thirds of the complications occurred within one year of RT and about 88.9% of complications occurred within two years of RT initiation. This is consistent with results of long term complication analysis of patients with immediate breast reconstruction followed by adjuvant RT reported by Sacott *et al.* (27), showing 68.3% of complications occurring within one year of RT and 81.7% of complications occurring within two years of RT.

In this study, we analyzed the relationship between complications and patient and treatment factors, including RT factor. We did not find any statistically significant factor. It is known that DM, BMI (> 30), chemotherapy and bilateral surgery are associated with complication occurrence in patients who

underwent breast reconstruction and adjuvant RT (20-22, 26). In this study however, DM and obesity were not significantly associated with complication. It is probably due to small number of patients who have DM or BMI ≥ 30 . Also chemotherapy has been reported to increase postoperative complications (26), so, as chemotherapy was performed in all patients in this study, we analyzed complications related to chemotherapy timing (neoadjuvant/adjuvant); there was no significant effects. Regarding the reconstruction flap type, there was no significant difference between the three flaps. This is consistent with the study by Garvey *et al.* (28) showing no significant difference in DIEP flaps and muscle sparing free TRAM flaps in relation to fat necrosis in patients with PMRT. Chang et al, who studied 446 irradiated flaps, also showed no difference in early and late complications between flaps (29). The use of bolus, boost RT and RT field did not show any significant difference in occurrence of complication as in other studies (6,19). In the present study, DHI, flap size (g) and chest wall CTV (cm³) were analyzed for the first time. High DHI (>1.4) and high chest wall CTV (> 687 cc) were didn't showed significant correlation with complication. In flap size, high flap size group (≥ 1538.6 g) showed distinct lower 2-year CFS comparing to small flaps size group, but with no statistical significance (92.9% vs. 75.7%, p=0.159). However, because this study included a relatively small numbers of patients and events, these factors should be further investigated in future studies.

This study has several limitations. First, its retrospective nature imposed limitations in the evaluation of complications as complication assessment was performed based on medical records. Second, there might be selection bias due to the limited number of patients and few events. Third, fibrosis and cosmetic outcomes, which are known to be major problems in long-term complication of RT, were not investigated. Finally, as follow-up duration was relatively short, some complications might not have been included. However, this study analyzed the patients who underwent immediate reconstruction using only autologous tissue,

excluding patients who used tissue expander or prosthetic implant and autologous tissue together. Since these patients showed

acceptable levels of complication rate after adjuvant RT, this study could be used as a reference when considering RT in such patients.

Table 5. Other studies reporting complication of patients treated with IABR and adjuvant radiotherapy.

Study	No. of pts	RT (Gy)	Median Follow-up (months)	Complication	Fat necrosis	Revision surgery	Aesthetic outcome
Adesiyun et al., 2011 ⁽¹⁵⁾	35	Median, 50.4 (45-50.4)	63.6	Early 8.6% Late 17.1%	11%	-	Aesthetic satisfaction, 67%
Mckeown et al., 2009 ⁽¹⁶⁾	13	Median, 50	51 (37 – 65)	-	15.4%	15.4%	Acceptable, 82.6%
Wong et al., 2008 ⁽¹⁷⁾	47	Median, 50.4 (45-54)	13 (2 – 58)	2- years *Major 15% Minor 29%	-	9%	-
Halyard et al., 2004 ⁽¹⁸⁾	15	50.4-60.6	26.4	-	13%	13%	Excellent/ good, 87%
Anderson et al., 2003 ⁽¹⁹⁾	35	50-50.4	28	†Major 0% ‡Minor 27%	17.1%	0%	Excellent/ good, 90%
Hunt et al., 1997 ⁽³⁰⁾	19	Median, 49.5 (45-50.4)	-	11%	10.5%	11%	Excellent/ good, Physician, 94%
This study, 2018	52	Median, 50.4 (50 -59.4)	22.3 (5.3-98.6)	Major 5.8% Minor 11.5%	15.4%	5.8%	-

Abbreviations: IABR, immediate autologous breast reconstruction; No., number; pts, patients. Data for patients who underwent immediate autologous breast reconstruction and adjuvant RT was extracted in the entire cohort of each study. *major complication, defined as requiring major corrective surgery (complete revision of a reconstruction, implant removal or replacement or surgical intervention for complication). †major complication, defined as requiring corrective surgery or loss of reconstruction. ‡minor complication, including infection, chest wall fibrosis, fat necrosis or contracture

CONCLUSION

The IABR followed by adjuvant RT may be a reasonable option in patients who underwent mastectomy, in terms of postoperative complication. Complications occur most frequently within 1 year after initiation of RT, and most complication occur within 2 years. The association of treatment factors with complication should be identified in further studies.

Ethical statement

This study was approved by the institutional ethics committee (Catholic Medical Center - institutional review board (IRB No. 2018-1409-0001).

Conflicts of interest: Declared none.

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