

Impact of radiation dose on complications among women with breast cancer who underwent breast reconstruction and post-mastectomy radiotherapy: A multi-institutional validation study

Seung Yeun Chung^{a,b}, Jee Suk Chang^a, Kyung Hwan Shin^{c,**}, Jin Ho Kim^c, Won Park^d, Haeyoung Kim^d, Kyubo Kim^e, Ik Jae Lee^f, Won Sup Yoon^g, Jihye Cha^h, Kyu-Chan Leeⁱ, Jin Hee Kim^j, Jin Hwa Choi^k, Sung-Ja Ahn^l, Boram Ha^m, Sun Young Leeⁿ, Dong Soo Lee^o, Jeongshim Lee^p, Sei One Shin^q, Sea-Won Lee^r, Jinhyun Choi^s, Mi Young Kim^t, Yeon Joo Kim^u, Jung Ho Im^v, Chang-Ok Suh^v, Yong Bae Kim^{a,*}

^a Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

^b Department of Radiation Oncology, Ajou University School of Medicine, Suwon, Republic of Korea

^c Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea

^d Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

^e Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, Republic of Korea

^f Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

^g Department of Radiation Oncology, Korea University Ansan Hospital, Korea University Medical College, Seoul, Republic of Korea

^h Department of Radiation Oncology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Republic of Korea

ⁱ Department of Radiation Oncology, Gachon University Gil Medical Center, Incheon, Republic of Korea

^j Department of Radiation Oncology, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Republic of Korea

^k Department of Radiation Oncology, Chung-Ang University Hospital, Seoul, Republic of Korea

^l Department of Radiation Oncology, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Republic of Korea

^m Department of Radiation Oncology, Hallym University Dongtan Sacred Heart Hospital, Hwasung, Republic of Korea

ⁿ Department of Radiation Oncology, Chonbuk National University Hospital, Jeonju, Republic of Korea

^o Department of Radiation Oncology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, Republic of Korea

^p Department of Radiation Oncology, Inha University Hospital, Inha University of Medicine, Incheon, Republic of Korea

^q Department of Radiation Oncology, Andong Medical Group Andong Hospital, Andong, Republic of Korea

^r Department of Radiation Oncology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

^s Department of Radiation Oncology, Jeju National University Hospital, Jeju, Republic of Korea

^t Department of Radiation Oncology, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea

^u Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

^v Department of Radiation Oncology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea

ARTICLE INFO

Article history:

Received 27 October 2020

Received in revised form

11 January 2021

Accepted 15 January 2021

Available online 20 January 2021

Keywords:

Breast cancer

Breast reconstruction

ABSTRACT

Purpose: Emerging data suggest that higher radiation doses in post-mastectomy radiotherapy may be associated with an increased risk of reconstruction complications. This study aimed to validate previous findings regarding the impact of radiation dose on complications among women with breast cancer using a multi-center dataset.

Methods: Fifteen institutions participated, and women with breast cancer who received radiotherapy after either autologous or prosthetic breast reconstruction were included. The primary endpoint was major post-radiation therapy complications requiring re-operation for explantation, flap failure, or bleeding control.

Results: In total, 314 patients were included. Radiotherapy was performed using both conventional fractionation and hypofractionation in various schedules. The range of the radiation therapy dose in

Abbreviations: CI, confidence interval; EQD2, equivalent dose in 2 Gy fractions; HER2, human epidermal growth factor receptor 2; MROC, Mastectomy Reconstruction Outcomes Consortium; OD, odds ratio; PMRT, post-mastectomy radiotherapy; RT, Radiotherapy.

* Corresponding author. Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea.

** Co-corresponding author. Department of Radiation Oncology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, Republic of Korea.

E-mail addresses: radiat@snu.ac.kr (K.H. Shin), ybkim3@yuhs.ac (Y.B. Kim).

<https://doi.org/10.1016/j.breast.2021.01.003>

0960-9776/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Major complication
Radiation therapy

Equivalent Dose in 2 Gy fractions (EQD2; $\alpha/\beta = 3.5$) varied from 43.4 to 71.0 Gy (median dose: 48.6 Gy). Boost radiation therapy was administered to 49 patients. Major post-radiation therapy complications were observed in 24 (7.6%) patients. In multivariate analysis, an increasing EQD2 per Gy (odds ratio [OR]: 1.58, 95% confidence interval [CI]: 1.26–1.98; $p < 0.001$), current smoking status (OR: 25.48, 95% CI: 1.56–415.65; $p = 0.023$), and prosthetic breast reconstruction (OR: 9.28, 95% CI: 1.84–46.70; $p = 0.007$) were independently associated with an increased risk of major complications.

Conclusion: A dose-response relationship between radiation dose and the risk of complications was validated in this multi-center dataset. In this context, we hypothesize that the use of hypofractionated radiotherapy (40 Gy in 15 fractions) may improve breast reconstruction outcomes. Our multi-center prospective observational study (NCT03523078) is underway to further validate this hypothesis.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The goal of breast reconstruction for women with breast cancer is to restore the breast mound and to improve the psychological consequences of mastectomy. The popularity of breast reconstruction has risen worldwide [1]. In patients with adverse features, such as node-positive breast cancer, post-mastectomy radiotherapy (PMRT) with regional node irradiation not only improves local control but also survival, as shown in numerous studies [2–5]. However, PMRT with regional node irradiation can be associated with increased toxicity such as the occurrence of fat necrosis in patients with autologous reconstruction and high mean internal mammary node dose [6]. Although PMRT often leads to poor cosmesis and satisfaction outcomes in women who undergo breast reconstruction [7], these issues have gradually been resolved with recent advances in reconstructive and radiotherapy (RT) techniques [8,9]. Therefore, a collaborative effort among surgeons and radiation oncologists is important to mitigate complications without increasing recurrence in the treatment of patients planning to undergo both breast reconstruction and PMRT. For example, the multidisciplinary ESTRO ACROP consensus guideline for target volume definitions for chest wall irradiation after mastectomy with immediate breast reconstruction was recently published [10].

Although efforts have been made in the field of surgery (e.g., microsurgical techniques and using an acellular dermal matrix) to reduce complications and improve patient satisfaction, the PMRT schedule has not changed much in the past decade (50 Gy using conventional fractionation) [11]. However, advances in RT technology supporting precise conformal RT and a greater understanding of breast cancer biology have diversified radiation treatments, from beam delivery to fractionation schedules. Previous studies [12,13] have shown that the practice patterns for PMRT differ significantly between physicians. Although one would hypothesize that different RT techniques varying in factors such as fractionation, RT modality, the use of bolus, boost RT, and internal mammary nodal RT may influence cosmetic complications, evidence concerning the impact of each of these factors is lacking.

In the setting of breast-conserving surgery, hypofractionated breast irradiation showed similar or even better cosmetic outcomes such as moderate or marked breast shrinkage, telangiectasia, dyspigmentation, and breast edema compared to conventional fractionation RT [14,15]. As for patients with mastectomy and breast reconstruction, Chang et al. [16] previously reported that the level of the radiation dose around the reconstructed breast is linked to the risk of reconstruction complications. The study suggested that a modification of RT treatment (e.g., by using a hypofractionated regimen or boost RT) could determine the maximum dose level and consequentially affect the complication rate. Considering that these analyses were conducted only in women who underwent two-stage prosthetic breast reconstruction at a single institution, we

designed the present retrospective study to validate the previous findings and to analyze the radiation dose-response relationship for reconstruction complications after RT in a multi-institutional cohort.

2. Materials and methods

2.1. Eligibility

A retrospective multi-center observational study of women with breast cancer who underwent RT and breast reconstruction at 15 institutions between 2015 and 2016 was conducted after approval from the review board of the Korean Radiation Oncology Group (KROG 18–04). Patients treated during 2015–2016 were included; breast reconstruction was actively performed during this period after reimbursement from the Korean National Insurance Service, which started in 2012. Another intention of including patients treated during 2015–2016 and not including more recently treated patients was to sufficiently observe reconstruction complications, since the overall treatment period may be 1–2 years in patients treated with mastectomy, adjuvant chemotherapy, adjuvant RT, and two-stage breast reconstruction. The eligibility criteria were histologically proven breast cancer, non-metastatic disease, female sex, breast reconstruction following mastectomy, and subsequent adjuvant RT. The exclusion criteria were bilateral breast cancer or loss to follow-up. After approval from each participating center, each center retrospectively reviewed the patients' medical charts and collected data. Treatment patterns were also collected, which varied widely among the institutions; the patterns of practice were analyzed separately in another report [17].

2.2. Endpoint and variables

The development of any breast reconstruction complications and major breast reconstruction complications was collected by medical chart review. Right or left side, which received curative surgery and RT, were included for analysis. All complication events that occurred during follow-up were included in this study and pre-RT breast complications and post-RT breast complications were seen separately. The primary endpoint was major reconstruction complications occurring after the completion of RT. Complication scale which was used by the prospective multi-center observational Mastectomy Reconstruction Outcomes Consortium (MROC) study was used [18]. Specific complications included seroma, hematoma, wound dehiscence, necrosis, bleeding, contracture, infection, cellulitis, rupture, exposure, rippling, malposition, and hernia. Complication data were collected by each site coordinator and were reviewed centrally. Major complications were defined as those requiring re-operation for explantation, flap failure, or bleeding control.

Patient-related variables included age, body mass index, smoking history, diabetes mellitus, and residential area (metropolitan vs. non-metropolitan and rural areas). Tumor- and surgery-related variables included clinical T and N stages, multicentricity, type of systemic therapy (none, chemotherapy, hormonal therapy, and anti-human epidermal growth factor receptor 2 [HER2] therapy), type of mastectomy (standard, skin sparing, or nipple sparing), and resection margin (clear, close, or positive). Reconstruction-related variables included breast reconstruction sequence (one-vs. two-stage), reconstruction timing (immediate vs. delayed), type of breast reconstruction (autologous vs. prosthetic), type of breast reconstruction at the time of RT (tissue expander, implant, transverse rectus abdominis musculocutaneous flap, deep inferior epigastric perforator flap, latissimus dorsi flap, or other), bilateral breast reconstruction, and operation time. Lastly, RT-related variables included RT technique (3D conformal RT, field-in-field, step-and-shot intensity-modulated RT, and volumetric arc therapy), radiation dose/fraction, estimated maximum dose to the chest wall on the RT planning system, chest wall boost RT, the use of bolus material, and the use of regional RT.

2.3. Statistical analyses

Since radiation dose schedules varied widely among the institutions, the radiation dose was calculated as an Equivalent Dose in 2 Gy fractions (EQD2) with an α/β ratio of 3.5 for equal comparisons of dose effects. The α/β ratio of 3.5 was estimated from START-A trial with breast shrinkage as the endpoint [15,19]. For analysis of postoperative breast complication rates after radiotherapy in Table 3, patients were divided into two groups by the median EQD2 dose 48.6 Gy. Complication rates among the groups were analyzed using chi-square or Fisher's exact tests. Univariate and multivariate analyses were performed using logistic regression, and a backward elimination method was used for the multivariate model. As for univariate and multivariate analyses, EQD2 dose (Gy) was included as a continuous variable. A dose-response relationship curve for major reconstruction complications was constructed from the logistic regression analysis. All analyses were performed using SPSS version 23.0 (IBM Inc., Armonk, NY, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

In total, 314 patients were included in the analysis. The baseline characteristics of the patients are summarized in Table 1. The median age was 44 years (range, 23–69 years), and the median body mass index was 22.6 kg/m² (range, 15.7–35.6 kg/m²). Four (1.3%) patients were current smokers. A total of 149 patients (47.5%) received neoadjuvant chemotherapy, and 187 patients (59.6%) received adjuvant chemotherapy. Two hundred thirty patients (73.2%) received endocrine therapy, and 39.8% of the patients received anti-HER2 therapy. The most common type of mastectomy was standard total mastectomy (163 patients, 51.9%). The types of breast reconstruction and RT treatment are shown in Table 2. Approximately half of the patients (160 patients, 51.0%) underwent one-stage breast reconstruction. All but two patients underwent immediate breast reconstruction; 60.5% underwent prosthetic breast reconstruction, whereas 38.9% underwent autologous breast reconstruction. All patients were diagnosed with unilateral breast cancer in this study and ten percent of patients underwent bilateral breast reconstruction. Various RT techniques were used; forward intensity-modulated RT (field-in-field) was the most common (40.4%), followed by volumetric arc therapy (28.7%). Conventional fractionation was used in two-thirds of patients. In the remaining third, hypofractionation was used with different treatment

Table 1

Baseline patient characteristics (N = 314).

		N	%
Age, years	Median (range)	44	23–69
	≤40	116	36.9%
	>40	198	63.1%
BMI, kg/m ²	Median (range)	22.6	15.7–35.6
	Yes	14	4.5%
	No	300	95.5%
Smoking	No	303	96.5%
	Yes, current smoker	4	1.3%
	Unknown	7	2.2%
Residential area	Metropolitan	219	69.7%
	Non-metropolitan	95	30.3%
Clinical T stage	T1	70	22.3%
	T2	152	48.4%
	T3–4	88	28.0%
	Tx	4	1.3%
Clinical N stage	N0	52	16.6%
	N+	260	82.8%
	Unknown	2	0.6%
Multicentricity	Yes	126	40.1%
	Unknown	1	0.3%
Systemic Tx		305	97.1%
Neoadjuvant chemo		149	47.5%
Adjuvant chemo		187	59.6%
Chemo regimen	T-based	226	72.0%
	A-based	14	4.5%
	Others	65	20.7%
Endocrine Tx		230	73.2%
Anti-HER2 Tx		125	39.8%
Mastectomy	Standard total	163	51.9%
	Skin sparing	74	23.6%
	Nipple sparing	77	24.5%
	Complete	276	87.9%
Resection margin	Close	23	7.3%
	Positive	12	3.8%
	Unknown	23	1.0%

Abbreviations: A, anthracycline; BMI, body mass index; chemo, chemotherapy; DM, diabetes mellitus; HER2, human epidermal growth factor receptor 2; T, taxane; Tx, treatment.

schedules. The most commonly used hypofraction regimen was 40.05 Gy in 15 fractions. The median radiation dose to the reconstructed breast in terms of EQD2 (α/β ratio: 3.5) was 48.6 (range, 43.4–71.0) Gy. Boost RT was administered to 15.6% of patients (median radiation dose: 9 [range, 3.6–21.0] Gy). Bolus was used in 53.5% of patients, depending on institutional preferences. The majority of patients (94.3%) received RT to the regional lymph nodes.

The postoperative breast complication rates are described in Table 3. Major postoperative complications occurred in 30 (9.6%) patients. Major pre- and post-RT complications occurred in 8 (2.5%) and 24 (7.6%) patients, respectively. Median time-to-event for major post-RT breast complication was 7.0 months (range, 0.1–27.0 months). At 6 months and 12 months post-RT, 9 patients and 18 patients experienced major post-RT breast complications, respectively. Postoperative breast complication rates were also described according to neoadjuvant chemotherapy and EQD2 dose groups. Patients who received a RT dose higher than EQD2 48.6 Gy had higher post-RT major complication rates than those who received lower RT doses (9.5% vs. 1.4%).

The results of the univariate and multivariate analysis of major post-RT complications are summarized in Table 4. After adjusting for other factors, increasing EQD2 dose per Gy (odds ratio [OR]: 1.58, 95% confidence interval [CI]: 1.26–1.98; $p < 0.001$), current smoking status (OR: 25.48, 95% CI: 1.56–415.65; $p = 0.023$), and prosthetic breast reconstruction (OR: 9.28, 95% CI: 1.84–46.70; $p = 0.007$) were independently associated with an increased risk of major complications. The dose-response relationship curve, shown

Table 2
Types of reconstructions and radiotherapy treatments.

	N	%
Reconstruction stage		
1-stage	160	51.0%
2-stage	154	49.0%
Reconstruction timing		
Immediate	312	99.4%
Delayed	2	0.6%
Reconstruction type		
Prosthetic-based	190	60.5%
ADM use	165	52.5%
Autologous-based	122	38.9%
Both	2	0.6%
Reconstruction status at the time of RT		
Tissue expander	151	48.1%
TRAM	75	23.9%
Implant	39	12.4%
DIEP	29	9.2%
LD	14	4.5%
Others	6	1.9%
Bilateral reconstruction	34	10.8%
Operation time, hour	Mean (SD)	6.1
RT technique		
Forward IMRT (Field-in-field)	124	40.4%
VMAT	90	28.7%
3D conformal	58	18.9%
Step-and-shoot IMRT	26	8.3%
Helical tomotherapy	8	2.5%
2D (tangential)	1	0.3%
Unknown	7	2.2%
Fractionation		
1.8- or 2.0-Gy fractionation	209	66.6%
≥45 Gy and <50 Gy	8	2.5%
50 or 50.4 Gy	192	61.1%
>50 Gy	9	2.9%
Hypofractionation	105	33.4%
40.05 Gy in 15 fractions	55	17.5%
42.56 Gy in 16 fractions	11	3.5%
45.9 Gy in 17 fractions	19	6.1%
48 Gy in 20 fractions	14	4.5%
Others	3	1.0%
RT dose in EQD2, Gy (alpha/beta ratio, 3.5)	Median (range)	48.6 (43.4–71.0)
Use of boost RT		
Maximum doses within the PTV, %	Mean (SD)	107.6% 5.8%
Use of bolus		168 53.5%
Use of regional RT		296 94.3%
Inclusion of IMN		163 51.9%

Abbreviations: ADM, acellular dermal matrix; DIEP, deep inferior epigastric perforators flap; EQD2, equivalent dose in 2 Gy fractions; IMN, internal mammary node; IMRT, intensity-modulated radiation therapy; LD, latissimus dorsi muscle flap; PTV, planning target volume; RT, radiation therapy; SD, standard deviation; TRAM, transverse rectus abdominis myocutaneous flap; VMAT, volumetric arc therapy.

in Fig. 1, shows an increase in the probability of post-RT major complication as the EQD2 dose increases.

Table 3
Postoperative breast complication rates after neoadjuvant chemotherapy and radiotherapy.

	Total		Before RT		After RT	
	Any	Major**	Any	Major**	Any	Major**
Total Group	106 (33.8)	30 (9.6)	44 (14.0)	8 (2.5)	79 (25.2)	24 (7.6)
Neoadjuvant chemotherapy						
No	54 (32.7)	14 (8.5)	25 (15.2)	6 (3.6)	39 (23.6)	9 (5.5)
Yes	52 (34.9)	16 (10.7)	19 (12.8)	2 (1.3)	40 (26.8)	15 (10.1)
EQD2, Gy (alpha/beta ratio, 3.5)						
< Median	27 (37.0)	1 (1.4)*	10 (13.7)	0 (0.0)	19 (26.0)	1 (1.4)*
≥ Median	79 (32.8)	29 (12.0)*	34 (14.1)	8 (3.3)	60 (24.9)	23 (9.5)*

*p < 0.05.

**Major complications were defined as those requiring re-operation for explantation, flap failure, or bleeding control.

Abbreviations: EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy.

As additional analysis, multivariate analyses of major post-RT complications were performed for each prosthetic-based and autologous-based groups. Radiotherapy dose in EQD2 was a significant factor for the prosthetic-based reconstruction group (OR: 1.58, 95% CI: 1.27–1.95; p < 0.001). In contrast, radiation therapy dose in EQD2 was not a significant factor for the autologous-based group (p = 0.780).

4. Discussion

In accordance with the global trend toward the restoration of both physical and emotional health by breast reconstruction, the proportion of patients undergoing breast reconstruction who received RT has increased markedly in Korea since 2012, when reimbursement from the Korean National Insurance Service started [16,20,21]. Following a previous single-center study, we conducted a retrospective multi-center observational analysis of 314 patients with breast cancer who underwent RT and breast reconstruction at 15 institutions between 2015 and 2016.

In this study, the rates for any complications and major complications were 38.0% and 13.5%, respectively, for irradiated patients who underwent prosthetic breast reconstruction. For irradiated patients who underwent autologous breast reconstruction, the rates for any complication and major complications were 27.0% and 3.0%, respectively. These were slightly lower but consistent with the findings from the MROC study, a prospective cohort study, which aimed to evaluate and compare outcomes such as complications and postoperative pain in patients who underwent breast reconstruction after mastectomy. The MROC study reported any breast complication rates of 38.9% and 25.6%, respectively, in irradiated patients with implant reconstruction and with autologous reconstruction; in comparison, the rates were 21.8% and 28.3% in unirradiated patients. Rates of reconstruction failure were 18.7% and 1.0%, respectively, in patients with implant reconstruction and with autologous reconstruction, as compared to 3.7% and 2.4% in unirradiated patients [18,22,23]. This discrepancy may be explained by the fact that a small percentage of our patients underwent bilateral breast reconstruction (10.8%) and that a larger portion of patients had lower BMI. In the MROC study, bilateral breast reconstruction and high BMI were identified as risk factors for complications [18]. Thus, the cohort of this study may be less susceptible to breast complications compared to cohorts observed in Western countries (45% of patients underwent bilateral breast reconstruction and 30.7% had BMI higher than 30 kg/m² in the MROC study).

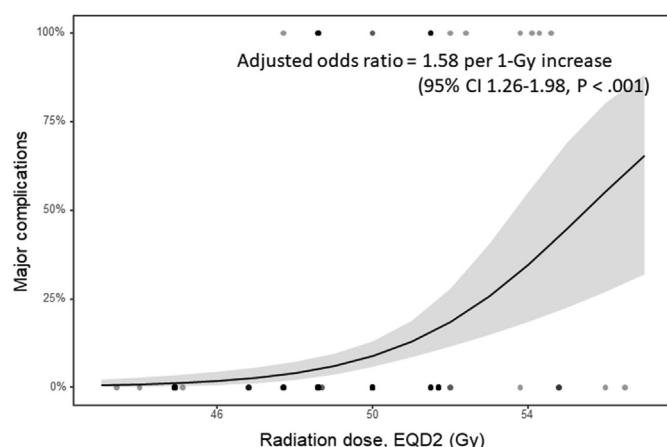
In patients who received PMRT in the present study, the total radiation dose received, current smoking status, and prosthetic breast reconstruction were identified as independent risk factors for the development of major post-RT breast complications. Our

Table 4

Univariate and multivariate analyses of factors associated with major post-radiotherapy complications.

Variable	UVA	MVA		
	p	OR	95% CI	p
Age	0.399			
BMI	0.458			
DM (yes vs. no)	0.999			
Smoking (yes vs. no)	0.225	25.48	1.56–415.65	0.023
Neoadjuvant chemotherapy (yes vs. no)	0.130			
Adjuvant chemotherapy (yes vs. no)	0.760			
Reconstruction type (Prosthetic vs. Autologous)	0.006	9.28	1.84–46.70	0.007
Reconstruction timing (Immediate vs. Delayed)	0.999			
Reconstruction stage (2-stage vs. 1-stage)	0.002			
Bilateral reconstruction (yes vs. no)	0.962			
Radiotherapy dose in EQD2, Gy	0.005	1.58	1.26–1.98	<0.001
Boost RT (yes vs. no)	0.465			
Fractionation (Hypofraction vs. Conventional)	0.079			
Time interval between reconstruction and RT, months	0.074	0.87	0.73–1.04	0.130

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; EQD2, equivalent dose in 2 Gy fractions; MVA, multivariate analysis; OR, odds ratio; RT, radiation therapy; UVA, univariate analysis.

**Fig. 1.** Dose-response relationship curve for major reconstruction complications.

finding with respect to the positive correlation of radiation dose with complication risk is novel. This multi-center study included patients who were treated with a wide range of hypofractionated regimens, which facilitated the analysis of the dose-response relationship. Muresan et al. [24] first reported that patients with less dose inhomogeneity (maximum dose, 58.5 Gy) due to prone positioning technique had fewer complications than those with greater dose inhomogeneity (maximum dose, 61.7 Gy). This finding was corroborated by Chang et al. [16], who showed that as the near maximum radiation dose increased, the risk of complications increased, with an OR of 1.12 per 1-Gy increase. The authors found that the administration of 40–42.56 Gy in 15 or 16 fractions via a hypofractionated regimen or sparing boost RT plays a major role in reducing near maximum dose-related complications. In the current study, boost RT was performed generally in patients with positive or close margins upon institutional preferences. Overall 15.6% of the patients received boost RT, which is a fairly small percentage compared to a US survey in 2014, in which 66.5% of responders answered that they would prescribe boost RT [25]. Recently, Naoum et al. [26] investigated the impact of the addition of chest wall boost RT on breast reconstruction morbidity. The study included 750 women (381 who received chest wall boost RT and 369 who did not) who underwent all types of breast reconstruction during 1997–2016. The authors found that chest wall boost RT was associated with an increased risk of complications, including infection

and skin necrosis (OR: 2.2–2.6). Our results are consistent with these findings, which provides further evidence for a dose-response relationship.

In the United States, a phase III randomized trial (A221505) has been initiated by the Alliance group to compare the reconstruction complication rate of a hypofractionated regimen using 42.56 Gy in 16 fractions with those of conventional fractionated regimens. In Korea, we have also initiated a prospective multi-center study (NCT03523078) to assess patient-reported outcomes and reconstruction complication rates in patients who have undergone breast reconstruction. Radiation details, including dose fractionation schedules, dose inhomogeneity, and chest wall boost RT, will be collected to investigate the dose-response relationship.

Smoking is known to increase the risk of surgical complications, and continuing to smoke during RT leads to further problems [27]. Considering that smoking cessation greatly reduces the risk of radiation-induced heart disease, patients should be informed of the combined risk of breast complications from smoking and RT, and the benefits of smoking cessation should be emphasized [28]. In this study, smoking showed to be a significant adverse factor for major post-RT breast complications. However, a limitation for this analysis would be that only four patients were smokers in this study.

Furthermore, in this study, patients who underwent prosthetic breast reconstruction had an increased risk of major post-RT breast complications (OR: 9.49, 95% CI: 1.85–48.65). These findings are consistent with the results of a meta-analysis of four retrospective studies and the prospective MROC study [22,29]. In the meta-analysis by Barry et al. [19], autologous breast reconstruction was associated with a reduced risk of complications than prosthetic reconstruction in patients who underwent RT (OR: 0.20, 95% CI: 0.11–0.39). In the prospective MROC study [18], RT was associated with a significant increase in the risk of 2-year complications in patients who underwent implant reconstruction (OR: 2.64, 95% CI: 1.77–3.94) but not in those who underwent autologous reconstruction (OR: 1.12, 95% CI: 0.66–1.92). Similarly, radiotherapy dose in EQD2 remained as a significant factor in the prosthetic-based reconstruction group, but lost its significance in the autologous-based reconstruction group in this study. However, several other benefits of prosthetic breast reconstruction (e.g., operative time and salvage options after reconstruction failure) could outweigh the risk of complications in some patients with low susceptibility (e.g., non-smoking status, non-obese status, and unilateral breast reconstruction) [23,30].

Recently, ESTRO ACROP consensus guideline for target volume delineation for patients who received post mastectomy radiotherapy after implant-based immediate reconstruction for early stage breast cancer was published [10]. Subsequent dosimetric studies are performed using the new guideline, including one study which showed significant dose reduction for normal heart and left anterior descending artery with the new target volume [31]. More studies reporting the association with the new guideline and reconstruction complications are anticipated.

There are several limitations to this study. First, since this is a multi-center retrospective study which collected data by medical chart review from each institution, limitations arising from data collection and different follow-up periods may exist. Secondly, the surgeon factor is universally considered as the most important factor affecting the complication rate. It would have been intriguing if our current study included unirradiated patients with breast reconstruction to take into account the different surgical technique by physician or institution and intra- and inter-surgeon variability. Another limitation of the dose-response relationship analysis was that a large proportion (29.6%) of the maximum dose data was missing in instances where a composite plan could not be created. This made the investigation of the independent impact of dose inhomogeneity on the complication rate impossible. Because of insurance coverage issues in Korea, bilateral reconstruction was seldom performed in our patients. Discrepancies in body mass index, smoking rates, comorbidities, breast cup size, and desired cup size between Korean women and their American counterparts should also be taken into consideration when interpreting our findings. In addition, both prosthetic-based and autologous-based reconstruction patients were included in this study. Further elaborate studies concerning each types of reconstruction separately are needed.

5. Conclusions

In conclusion, smoking, prosthetic breast reconstruction, and a higher total cumulative radiation dose were independent risk factors for major complications in this study. Our findings suggest that there is room for improvement in reducing major reconstruction complications, even at the time of RT, through smoking cessation and by using a hypofractionation regimen (40 Gy in 15 fractions). Further studies are warranted to validate these hypothetical results. An ongoing prospective multi-center observational study (NCT03523078) in Korea may help guide radiation oncologists and breast reconstruction surgeons in optimizing patient outcomes in this clinical setting.

Funding

This study was supported by the Research Grant of the Korean Foundation for Cancer Research (Grant number: 2017-B-3).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Informed consent

The requirement for written informed consent was waived owing to the retrospective nature of the study.

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

None.

Acknowledgments

None.

References

- [1] Panchal H, Matros E. Current trends in postmastectomy breast reconstruction. *Plast Reconstr Surg* 2017;140:75–135.
- [2] Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen M-B. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997;337:949–55.
- [3] McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* (London, England) 2014;383.
- [4] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015;373:317–27.
- [5] Thorsen LBJ, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, Zimmermann SJ, Brodersen H-J, Overgaard M, Overgaard J. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016;34:314–20.
- [6] Kaidar-Person O, Eblan MJ, Caster JM, Shah AR, Fried D, Marks LB, Lee CN, Jones EL. Effect of internal mammary vessels radiation dose on outcomes of free flap breast reconstruction. *Breast J* 2019;25:286–9.
- [7] Brownlee Z, Garg R, Listo M, Zavitsanos P, Wazer DE, Huber KE. Late complications of radiation therapy for breast cancer: evolution in techniques and risk over time. *Gland Surg* 2018;7:371.
- [8] Chu CK, Davis MJ, Abu-Ghname A, Winocour SJ, Losken A, Carlson GW. Implant reconstruction in nipple sparing mastectomy. *Semin Plast Surg* 2019;33:247–57. 04.
- [9] Houvenaeghel G, Bannier M, Rua S, Barrou J, Heinemann M, Knight S, Lambaudie E, Cohen M. Robotic breast and reconstructive surgery: 100 procedures in 2-years for 80 patients. *Surg Oncol* 2019;31:38–45.
- [10] Kaidar-Person O, Offersen BV, Hol S, Arenas M, Aristei C, Bourcier C, Cardoso MJ, Chua B, Coles CE, Damsgaard TE. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. *Radiother Oncol* 2019;137:159–66.
- [11] Gravina PR, Pettit RW, Davis MJ, Winocour SJ, Selber JC. Evidence for the use of acellular dermal matrix in implant-based breast reconstruction. *Semin Plast Surg* 2019;33:229–35. 04.
- [12] Mayadev J, Einck J, Elson S, Rugo H, Hwang S, Bold R, Daroui P, McCloskey S, Yashar C, Kim D. Practice patterns in the delivery of radiation therapy after mastectomy among the University of California Athena Breast Health Network. *Clin Breast Canc* 2015;15:43–7.
- [13] Koulis T, Dang A, Speers C, Olson R. Factors affecting radiotherapy prescribing patterns in the post-mastectomy setting. *Curr Oncol* 2018;25:e146.
- [14] Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, Stenbygaard L, Mjaaland I, Schreiber A, Kasti U-M. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: the DBCG HYPO trial. *J Clin Oncol* 2020;38:3615–25.
- [15] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–94.
- [16] Chang JS, Oh JH, Song SY, Lew DH, Roh TS, Kim SY, Keum KC, Lee DW, Kim YB. Influence of radiation dose to reconstructed breast following mastectomy on complication in breast cancer patients undergoing two-stage prosthetic breast reconstruction. *Frontiers in oncology* 2019;9:243.
- [17] Yang G, Chang JS, Shin KH, Kim JH, Park W, Kim H, Kim K, Lee IJ, Yoon WS, Cha J. Post-mastectomy radiation therapy in breast reconstruction: a patterns of care study of the Korean Radiation Oncology Group. *Radiation Oncology Journal* 2020;38:236–43.
- [18] Jaggi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, Pusic AL, Wilkins EG. Impact of radiotherapy on complications and patient-reported outcomes after

- breast reconstruction. *J Natl Cancer Inst*: *J Natl Cancer Inst* 2017;110:157–65.
- [19] Ray K, Sibson N, Kiltie A. Treatment of breast and prostate cancer by hypofractionated radiotherapy: potential risks and benefits. *Clin Oncol* 2015;27:420–6.
- [20] Hong KY, Son Y, Chang H, Jin US. Trends in breast reconstruction: implications for the national health insurance Service. *Archives of plastic surgery* 2018;45:239.
- [21] Kang SY, Kim YS, Kim Z, Kim HY, Kim HJ, Park S, Bae SY, Yoon KH, Lee SB, Lee SK, Jung K-W, Han J, Youn HJ. Breast cancer statistics in Korea in 2017: data from a breast cancer registry. *J Breast Cancer* 2020;23.
- [22] Wilkins EG, Hamill JB, Kim HM, Kim JY, Greco RJ, Qi J, Pusic AL. Complications in postmastectomy breast reconstruction one-year outcomes of the mastectomy reconstruction outcomes consortium (MROC) study. *Ann Surg* 2018;267:164.
- [23] Santosa KB, Qi J, Kim HM, Hamill JB, Wilkins EG, Pusic AL. Long-term patient-reported outcomes in postmastectomy breast reconstruction. *JAMA surgery* 2018;153:891–9.
- [24] Muresan H, Lam G, Cooper BT, Perez CA, Hazen A, Levine JP, Saadeh PB, Choi M, Karp NS, Ceradini DJ. Impact of evolving radiation therapy techniques on implant-based breast reconstruction. *Plast Reconstr Surg* 2017;139:1232e–9e.
- [25] Thomas K, Rahimi A, Spangler A, Anderson J, Garwood D. Radiation practice patterns among United States radiation oncologists for postmastectomy breast reconstruction and oncoplastic breast reduction. *Practical Radiation Oncology* 2014;4:466–71.
- [26] Naoum GE, Salama L, Ho A, Horick NK, Oladeru O, Abouegylah M, Daniell K, MacDonald S, Arafat WO, Smith BL. The impact of chest wall boost on reconstruction complications and local control in patients treated for breast cancer. *Int J Radiat Oncol Biol Phys* 2019;105:155–64.
- [27] Grønkjær M, Eliassen M, Skov-Ettrup LS, Tolstrup JS, Christiansen AH, Mikkelsen SS, Becker U, Flensburg-Madsen T. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. *Ann Surg* 2014;259:52–71.
- [28] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98.
- [29] Barry M, Kell M. Radiotherapy and breast reconstruction: a meta-analysis. *Breast Canc Res Treat* 2011;127:15–22.
- [30] Roje Z, Roje Z, Janković S, Ninković M. Breast reconstruction after mastectomy. *Coll Antropol* 2010;34:113–23.
- [31] Chang KH, Chang JS, Park K, Chung SY, Kim SY, Park RH, Han MC, Kim J, Kim H, Lee H. A retrospective dosimetric analysis of the new ESTRO-ACROP target volume delineation guidelines for postmastectomy volumetric modulated arc therapy after implant-based immediate breast reconstruction. *Frontiers in Oncology* 2020;10:2171.