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Original Article

Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: Initial report of reconstruction outcomes and predictors of complications

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ABSTRACT

Purpose: To report reconstructive outcomes of patients treated with post-mastectomy intensity modulated proton therapy (IMPT) following immediate breast reconstruction (IBR).
Materials and methods: Consecutive women with breast cancer who underwent implant-based IBR and post-mastectomy IMPT were included. Clinical characteristics, dosimetry, and acute toxicity were collected prospectively and reconstruction complications retrospectively.
Results: Fifty-one women were treated between 2015 and 2017. Forty-two had bilateral reconstruction with unilateral IMPT. The non-irradiated contralateral breasts served as controls. Conventional fractionation (median 50 Gy/25 fractions) was administered in 37 (73%) and hypofractionation (median 40.5 Gy/15 fractions) in 14 (27%) patients. Median mean heart, ipsilateral lung V20Gy, and CTV-IMN V95% were 0.6 Gy, 13.9%, and 97.4%. Maximal acute dermatitis grade was 1 in 32 (63%), 2 in 17 (33%), and 3 in 2 (4%) patients. Surgical site infection (hazard ratio [HR] 13.19, 95% confidence interval [CI] 1.67–104.03, $p = 0.0012$), and unplanned surgical intervention (HR 9.86, 95% CI 1.24–78.67, $p = 0.0068$) were more common in irradiated breasts. Eight of 51 irradiated breasts and 2 of 42 non-irradiated breasts had reconstruction failure (HR 3.59, 95% CI 0.78–16.41, $p = 0.084$). Among irradiated breasts, hypofractionation was significantly associated with reconstruction failure (HR 4.99, 95% CI 1.24–20.05, $p = 0.024$), as was older patient age (HR 1.14, 95% CI 1.05–1.24, $p = 0.002$).
Conclusions: IMPT following IBR spared underlying organs and had low rates of acute toxicity. Reconstruction complications are more common in irradiated breasts, and reconstructive outcomes appear comparable with photon literature. Hypofractionation was associated with higher reconstruction failure rates. Further investigation of optimal dose-fractionation after IBR is needed.
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The management of breast cancer requires multi-disciplinary collaboration in order to optimize oncologic outcomes and quality of life. Administration of post-mastectomy radiotherapy (PMRT) is indicated for some patients treated with mastectomy with clinical and pathologic risk factors associated with recurrence [1–4]. Recently, the rates of mastectomy and contralateral prophylactic mastectomy for breast cancer have been on the rise for both early stage and locally advanced breast cancer [5–8]. This trend has been accompanied by an increase in immediate breast reconstruction (IBR), which has a number of psychosocial advantages for patients [9,10]. However, IBR can present unique challenges for PMRT delivery in patients with indications for treatment [11]. Furthermore, PMRT after IBR significantly increases the risk of reconstruction complications, such as infection, wound dehiscence, mastectomy flap necrosis, capsular contracture, or poor esthetic outcome [12–17]. PMRT may also increase the risk reconstruction failure, commonly defined as tissue expander or implant removal, resulting in no final reconstruction or autologous reconstruction [12–18].

Proton therapy is a potentially attractive modality for the delivery of PMRT. The main advantage of proton therapy is believed to be a reduction in radiation exposure to normal tissues, such as the

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heart and lungs, which has been associated with late cardiac events and death from secondary cancers [19,20]. Proton therapy may also enable fewer compromises in clinical target volume (CTV) coverage. For example, internal mammary lymph node target coverage increases the dose to the underlying heart and lungs, often mandating compromises in target coverage to meet normal tissue constraints with conventional techniques [21,22]. These CTV compromises, which may increase the risk of recurrence, are more easily avoided with proton therapy [23–28]. The dosimetric benefits of proton therapy may be even more pronounced in patients with implant-based IBR and particularly those with bilateral reconstruction [29]. However, to date there are limited clinical data describing the reconstructive outcomes and quality of life in women who have undergone mastectomy, alloplastic IBR, and treated with adjuvant proton PMRT.

We previously reported the feasibility of intensity modulated proton therapy (IMPT) for PMRT delivery in women who had undergone IBR with tissue expanders with metallic ports [30]. In contrast with passive scattering proton therapy, IMPT delivered with pencil-beam scanning enables modulation of the proton dose at the skin surface to reduce hot spots over the reconstructed breast mound while still delivering a dose to the dermal lymphatics that would be expected to control microscopic disease. We hypothesized that this treatment approach would result in promising dosimetry, acute and late dermatologic toxicity and reconstruction outcomes. The purpose of this study is to report adverse events, reconstruction complications and predictors of toxicity in women with breast cancer treated with mastectomy, alloplastic IBR and IMPT.

Materials and methods

Patient selection

Proton therapy is discussed and offered to patients with IBR and indications for comprehensive regional nodal irradiation as part of clinical trials or our prospective registry. After institutional review board (ethics committee) approval, we identified consecutive women with breast cancer in our prospective registry who underwent immediate implant-based breast reconstruction and post-mastectomy IMPT at our institution between August, 2015 and October, 2017. Patients who underwent either IBR or radiotherapy at an outside facility were excluded.

Mastectomy and IBR technique

Mastectomy techniques utilized included nipple-sparing, areola-sparing and skin-sparing mastectomy. All patients underwent two-stage tissue expander-based IBR, except two patients who underwent single-stage implant based reconstruction. Our institutional alloplastic IBR technique has been described previously [31]. Briefly, patients underwent mastectomy with subsequent placement of tissue expanders with an integrated metallic injection port either prepectorally or subpectorally. The decision for prepectoral vs subpectoral reconstruction was based on surgeon and patient preferences. Acellular dermal matrices [AlloDerm RTU (LifeCell Corp. Branchburg, N.J.)] were used to support the tissue expander/implant and define the breast pocket. Tissue expander inflation with saline was initiated approximately 2 weeks postoperatively and completed prior to simulation. The second stage permanent implant exchange was usually performed at least 6 months after completion of IMPT. Fat grafting was simultaneously performed at the time of implant exchange in most cases to improve contour and/or mastectomy flap thickness.

Radiotherapy techniques

Simulation was typically scheduled approximately 6 weeks after mastectomy and IBR for patients who did not receive postoperative chemotherapy, or 3–4 weeks after last dose of chemotherapy for those who did receive postoperative chemotherapy. Our immobilization, computed tomography (CT) simulation, treatment planning, and techniques to account for the dosimetric impact of metallic ports within tissue expander were described previously [30].

Planning CT scans were routinely obtained in free breathing. However, in cases of unfavorable anatomy a deep-inspiratory breath hold (DIBH) technique was utilized ($n = 9$) in order to displace the heart posteriorly and caudally away from the CTV. The CTV included the reconstructed chest wall, levels one, two, and three of the axilla, the supraclavicular lymph nodes (SCV), and the internal mammary lymph nodes (IMNs). The CTV resembled the Radiation Therapy Oncology Group (RTOG) Breast Cancer Atlas with some notable exceptions based on previously published nodal mapping studies. The chest wall CTV routinely did not extend deeper than the anterior surface of the ribs and intercostal muscles except in the vicinity of the IMNs or if these structures were clinically involved [32]. The chest wall CTV excluded the first 3 mm of tissue under the skin. Supraclavicular target volumes routinely included both the medial and lateral supraclavicular lymph nodes. However, the supraclavicular CTV was not routinely extended medial to the lateral border of the internal carotid artery in order to reduce the dose to midline organs such as the esophagus and trachea as nodal recurrences and presentations are extremely unusual in that location [33–35]. Finally, the internal mammary lymph node (IMN) target volume was defined as a 4–5 mm medial and lateral expansion on the internal mammary vessels and extended from the cranial CT slice of the fourth rib to the most caudal extent of the supraclavicular volume near the junction of the internal mammary and brachiocephalic veins [36].

The median prescription dose was 50 Gy (range 40.5–57.5 Gy radiobiological effectiveness [RBE] = 1.1 delivered in 25 (range 15–25) daily fractions). Patients receiving hypofractionation were treated as part of MC1631, a randomized trial of 15 fraction vs 25 fraction pencil-beam scanning proton radiotherapy (NCT02783690). Treatment planning and delivery were identical for patients treated with conventional or hypofractionated IMPT on or off MC1631. Simultaneous integrated lymph node boosts, most commonly 56.25 Gy in 25 fractions, were permitted for patients with clinically involved and undissected internal mammary, infraclavicular or supraclavicular lymph nodes. Chest wall boosts were not administered. Treatment was delivered with a median of two anterior fields angled 45–60 degrees apart. Plans were evaluated for robustness to ensure CTV coverage under worst case uncertainty scenarios of ±5 mm isocenter shifts in x, y, and z directions and ±3% range uncertainty. Robust optimization features in the nonlinear universal proton optimizer were available to the dosimetrist and used at their discretion to achieve the desired robustness. The target coverage goal for the CTVs was D90% (minimum dose covering 90% of the target volume) $\geq$90% of the prescription dose under the worst case scenario of the robustness checks and D0.01 cm^3 (maximum dose to 0.01 cm^3 of the target volume) $\leq$110% of the prescription dose. The priority 2 goal for CTV coverage was D95% >95%. The skin was defined as the first 3 mm of tissue under the body surface and is considered both a target and an organ at risk during treatment planning. To ensure adequate coverage of the dermal lymphatics but to limit the risk of dermatologic toxicity treatment planning objectives for the skin included D90% $\geq$90%, and D1cc $\leq$105% for the skin overlying the chest wall and D1cc $\leq$90% for the skin overlying the supraclavicular CTV (Fig. 1).

All patients were treated with multi-field optimized pencil-beam scanning IMPT on a Hitachi PROBEAT-V proton therapy sys-

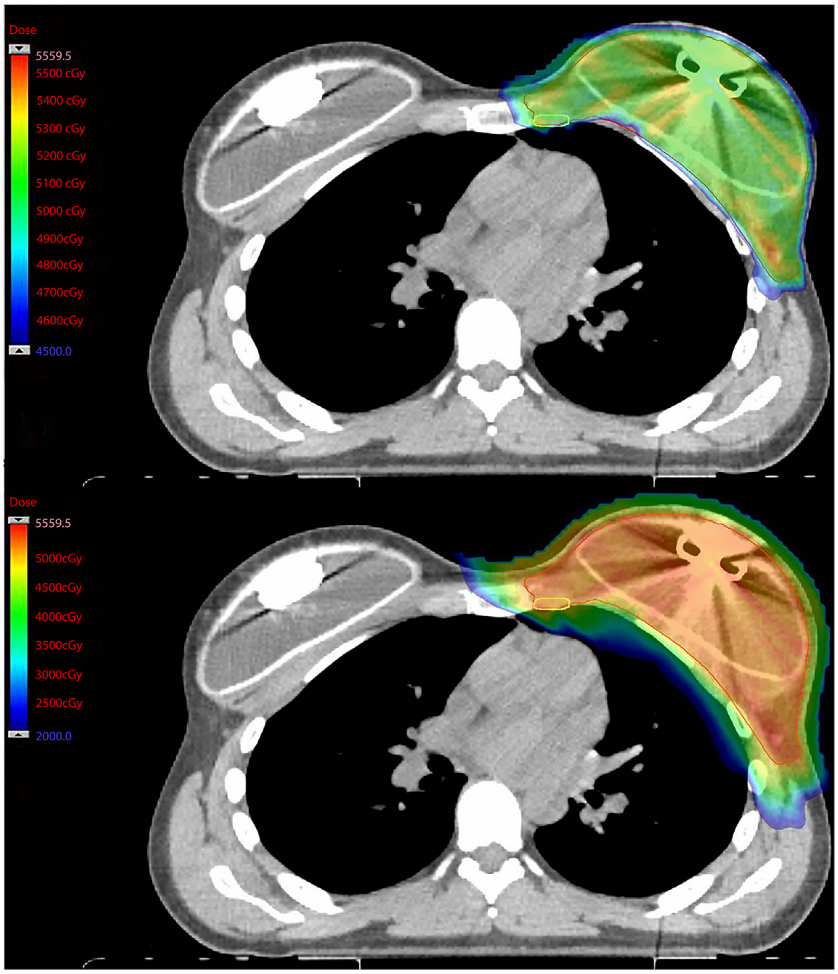

Fig. 1. Axial CT slice of the pencil-beam scanning proton therapy treatment plan of a representative patient with immediate tissue expander reconstruction. The 4500–5559 cGy color wash (top) and 2000–5559 cGy color wash (bottom) are shown. Chest wall and regional nodal CTV is contoured in red, internal mammary CTV is contoured in yellow.

tem (Hitachi, Tokyo, Japan) [30]. The spot size in air at the treatment beam energy varies depending on range shifter configuration, but is generally between 5 and 10 mm (1-sigma). To treat the shallow depths required, a range shifter was used with a 4.5 cm water-equivalent thickness. All plans were created in the Eclipse (Varian Medical Systems, Inc., Palo Alto, CA, USA) Treatment Planning System (RBE = 1.1), and verified in (1) an in-house graphics processing unit (GPU)-based Monte Carlo physical dose simulation (RBE = 1.1), and (2) an in-house Monte Carlo biologic dose simulation which assumes a linear relationship between RBE and linear energy transfer (LET) [37,38]. As part of the routine treatment planning process, plans generated by Monte Carlo biologic dose simulation were carefully evaluated for target coverage and increased RBE within OARs such as the brachial plexus and the chest wall, and modified as necessary to limit hot spots in these structures. Daily image guidance involved stereoscopic (oblique pair) kilovoltage imaging and 6-degree of freedom matching to the chest wall. Additionally, inter and intra-fraction tracking of the skin and body surface was performed using the AlignRT platform (Vision RT Inc., London, UK) [39].

Patients underwent at least one verification CT scan during the first week of therapy to assess for target volume coverage, dose to organs at risk (OARs), and the need for adaptive re-planning. Re-planning was performed at physician discretion for 5 of 51 patients, most commonly to reduce inhomogeneity and improve target coverage within the CTV.

Outcome measures

Acute radiotherapy adverse events were prospectively collected per common toxicity criteria for adverse events (CTCAE) version 4.0. Baseline patient characteristics and dosimetry were also collected prospectively. In addition, the following reconstruction complications were collected through retrospective chart review: surgical-site infection (SSI) and late infection were defined as infection requiring admission for intravenous antibiotics, culture positive infection or infection resulting in tissue expander or implant removal within one year of tissue expander or implant placement, or greater than one year of tissue expander or implant placement, respectively [31]; seroma, defined as a palpable fluid collection requiring intervention, such as aspiration, drainage or unplanned reoperation; mastectomy skin flap necrosis; wound dehiscence; capsular contracture, defined as Baker grade III or IV; hematoma; and tissue expander or implant removal. Reconstruction failure was defined as tissue expander or implant removal, resulting in no final reconstruction or autologous reconstruction [18].

Statistical analysis

Reconstruction complications are reported as hazard ratios and 95% confidence intervals with single variable associations using either Fine–Gray's competing risks hazard regression to account for complications due to distant metastasis or Firth's method of

analyzing rare events [40,41], as appropriate. This was only reported among ipsilateral irradiated breasts, as it was determined that ipsilateral breasts have more complications than contralateral non-irradiated breasts. Cumulative incidence of outcomes with respect to IMPT is also presented. This analysis was done using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Fifty-one women underwent mastectomy with alloplastic IBR and were treated with IMPT at our institution between 2015 and 2017. Forty-two of 51 women (82%) also underwent contralateral prophylactic mastectomy with IBR. Therefore, the outcomes of 93 implant-based reconstructions were evaluable (Fig. 2). Baseline patient characteristics and comorbidities are shown in Table 1. The median age was 49 (interquartile range [IQR] 44–58). The median body mass index (BMI) was 26 kg/m^2 (IQR 22–30 kg/m^2). Of the twelve (24%) patients with smoking history, 3 (6%) were current smokers at the time of breast cancer diagnosis, and 9 (18%) were former smokers. All patients were nicotine free for at least 6 weeks at time of surgery.

The majority of patients presented with clinical stage II (49%) or III (39%) breast cancer (Table 1). Invasive ductal carcinoma was the most prevalent histology (82%). Thirty-five (69%) patients had left-sided breast cancer, 14 (28%) had right-sided breast cancer, and 2 (4%) had bilateral breast cancer and underwent unilateral IMPT (one to the right breast, and one to the left breast). Chemotherapy was delivered in 43 (84%) patients. Neoadjuvant chemotherapy was used in 35 (69%) patients, 6 of whom (12%) also received post-operative chemotherapy. Adjuvant chemotherapy alone was used in 8 (16%) patients.

Treatment characteristics

Mastectomy and reconstruction techniques are displayed in Supplementary Table 1. Forty of 51 patients (78%) underwent prepectoral tissue expander placement and 11 (22%) underwent subpectoral tissue expander placement. Forty-two patients underwent bilateral mastectomy, among whom 33 (79%) underwent prepectoral tissue expander placement and 9 (21%) underwent subpectoral tissue expander placement.

Among the 37 patients who did not require post-operative chemotherapy, the median time from surgery to the initiation of IMPT was 56 (IQR 49–62) days. For those undergoing adjuvant chemotherapy, the median time from the completion of chemotherapy to the initiation of IMPT was 37 (IQR 27–69) days. Median follow up from the end of IMPT was 16 months (IQR 12–23).

Conventionally fractionated IMPT (median 50 Gy/25 fractions) was administered in 37 (73%) and hypofractionation (median 40.5 Gy/15 fractions) in 14 (27%) patients. Table 2 displays target coverage and doses to OARs. The median mean heart dose was 0.6 Gy for the entire cohort, 0.7 Gy in left-sided cases, and 0.4 Gy in right-sided cases. The median ipsilateral lung V20 Gy was 13.9%. These doses to OARs were achieved while maintaining target coverage to the IMNs (V90% = 98.5%) and the entire chest wall and regional nodal CTV (V95% = 99.7%).

Acute adverse events

Acute IMPT related adverse events are presented in Supplementary Table 2. Radiation dermatitis grading was as follows: 63% grade 1, 33% grade 2, and 4% grade 3. One patient developed pain and paresthesia of the ipsilateral upper extremity after the first fraction of IMPT which was classified as grade 1 brachial plexopathy by the treating physician. The etiology was ultimately determined to be prolonged immobilization during radiotherapy, and symptoms completely resolved with expectant management 3 months after completing IMPT. Four patients (3 grade 1, and 1 grade 2) developed esophagitis at the end of IMPT, and all resolved with conservative management.

Reconstruction complications and outcomes

The median follow-up was 19 months (IQR 15–26 months) from initial surgery. The median interval between mastectomy and permanent implant placement was 11 months (IQR 10–13 months) and the median interval between completion of IMPT and implant exchange was 7 months (IQR 6–9 months). By last follow-up, 44 (86%, including the two patients who underwent

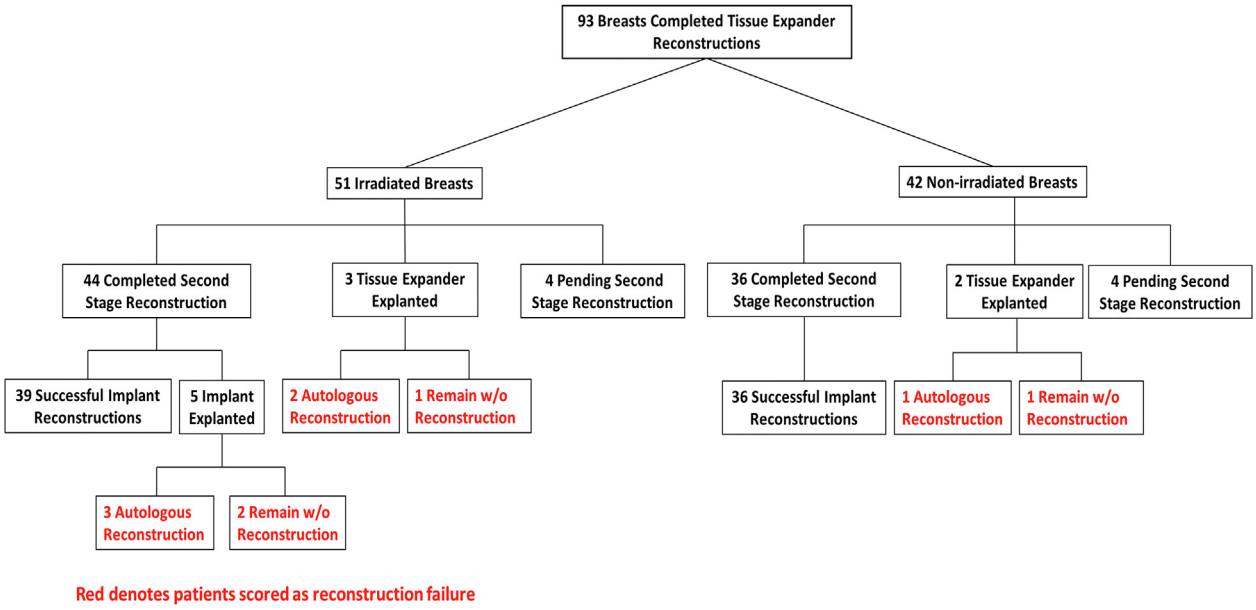

Fig. 2. Summary of the reconstruction outcomes of the irradiated and the non-irradiated reconstructed breasts.

Table 1
Patient, cancer and treatment characteristics.

Patient characteristics	Number of patient ($N = 51$)	Percent
Age at diagnosis		
30–39	10	19.6%
40–49	18	35.3%
50–59	14	27.5%
60–69	9	17.6%
BMI at diagnosis		
<18.5	1	2.0%
18.5–24.9	21	41.2%
25–29.9	18	35.3%
30–34.9	6	11.8%
>35	5	9.8%
Tobacco use at diagnosis		
Current smoker	3	5.9%
Former smoker	10	19.6%
Non-smoker	38	74.5%
Medical comorbidities at diagnosis		
Hypertension	7	13.7%
Diabetes	2	3.9%
Coronary artery disease	1	2.0%
Connective tissue disease	1	2.0%
Histology		
Invasive ductal carcinoma	37	72%
Invasive lobular carcinoma	8	16%
Both	5	10%
Mammary carcinoma	1	2%
Hormone receptors at diagnosis		
ER and/or PR+/HER2−	31	61%
ER−/PR−/HER2+	3	6%
ER and/or PR+ /HER2+	9	18%
ER−/PR−/HER2−	8	16%
Clinical stage at diagnosis		
Stage I	6	11.8%
Stage II	25	49.0%
Stage III	20	39.2%
Pathologic stage at surgery		
Stage 0	11	21.6%
Stage I	14	27.5%
Stage II	17	33.3%
Stage III	9	17.6%
Chemotherapy		
Neoadjuvant	29	56.9%
Adjuvant	8	15.7%
Neoadjuvant + Adjuvant	6	11.8%
No chemotherapy	8	15.7%
Axillary surgery		
Sentinel lymph node dissection	13	25.5%
Sentinel and axillary lymph node dissection	11	21.6%
Axillary lymph node dissection	27	52.9%

single-stage implant based reconstruction) of the 51 irradiated breasts and 36 (86%) of the 42 non-irradiated breasts had undergone exchange for a permanent implant. A summary of reconstruction outcomes is presented in Fig. 2.

Reconstruction complications are summarized in Table 3. Of the 51 irradiated reconstructed breasts, 20 (39%) had at least one complication compared with 5 (12%) of the non-irradiated reconstructed breasts. Complications (HR 3.31, 95% CI 1.23–8.94, $p = 0.01$), unplanned reoperation (HR 9.86, 95% CI 1.24–78.67, $p = 0.0068$), and SSI (HR 13.19, 95% CI 1.67–104.03, $p = 0.0012$) were significantly more common in irradiated, compared with non-irradiated reconstructed breasts (Fig. 3A–C). One patient with bilateral TE removal due to bilateral SSI had successful bilateral implant placement within 1 year of TE removal. One patient with removal of the irradiated TE due to late infection also had a new TE placed within 1 year of TE removal (Fig. 2). As a result, 8/51 (16%) irradiated breasts had reconstruction failure, compared with

Table 2
Radiotherapy dosimetric outcomes.

IMPT	Median	IQR
Prescription	50 Gy/25 fx	45 Gy/15 fx–50 Gy/25 fx
Maximum point dose	55 Gy	48–56 Gy
D0.01 cc [%]	109.7%	108.0–111.2%
D0.01 cc [Gy]	54.8 Gy	47.9–55.7 Gy
CTV D90 [%]	97.6%	96.5–99.0%
CTV V90% [%]	99.7%	99.3–99.9%
CTV D95 [%]	96.6%	95.0–98.0%
CTV V95% [%]	97.4%	95.0–99.0%
IMN D90 [%]	95.5%	92.1–97.8%
IMN V90% [%]	98.5%	94.0–99.9%
Ipsilateral lung V20Gy [%]	13.9%	10.1–14.9%
Ipsilateral lung Mean	7.3 Gy	6.5–8.3 Gy
Heart Mean	0.6 Gy	0.4–0.9 Gy
Heart V25 [%]	0.1%	0.0–0.3%
LAD Mean	2.8 Gy	1.5–4.0 Gy
RCA Mean	0.8 Gy	0.4–2.7 Gy

IMPT = intensity modulated proton therapy. Fx = fractions. IMN = internal mammary node. LAD: left anterior descending artery (for left-sided cases). RCA = right coronary artery (for right-sided cases).

Table 3
Reconstruction complications.

Complications	Irradiated breasts		Non-irradiated breasts $N = 42$ (%)
	Conventional fractionation $N = 37$ (%)	Hypofractionation $N = 14$ (%)	
Surgical site infection	7 (18.9%)	7 (50%)	1 (2.4%)
Late infection	1 (2.7%)	1 (7.1%)	0 (0%)
Seroma	2 (5.4%)	2 (14.3%)	1 (2.4%)
Hematoma	1 (2.7%)	0 (0%)	0 (0%)
Flap necrosis	2 (5.4%)	0 (0%)	1 (2.4%)
Contracture	0 (0%)	1 (7.1%)	0 (0%)
Wound dehiscence	0 (0%)	0 (0%)	2 (4.8%)
Reconstruction failure	3 (8.1%)	5 (35.7%)	2 (4.8%)

2/42 (5%) non-irradiated reconstructed breasts in which reconstruction was removed electively for symmetry (HR 3.59, 95% CI 0.78–16.41, $p = 0.08$, Fig. 3D).

Hypofractionation

Among the irradiated reconstructions, hypofractionation (HR 3.12, 95% CI 1.11–8.74, $p = 0.03$) was a significant risk factor for SSI (Supplementary Table 3, Supplementary Fig. 1). Hypofractionation (HR 4.73, 95% CI 1.39–16.11, $p = 0.01$) and elevated BMI (HR 1.11, 95% CI 1.02–1.22, $p = 0.02$) were significantly associated with unplanned reoperation (Supplementary Table 4, Supplementary Fig. 1).

Five of the 14 (36%) patients treated with hypofractionated IMPT experienced reconstruction failure, compared to 3 of 37 (8%) patients with conventionally fractionated IMPT (Table 3, Supplementary Fig. 1). Older age (HR 1.14, 95% CI 1.05–1.24, $p = 0.0019$), and hypofractionation (HR 4.99, 95% CI 1.24–20.05, $p = 0.024$) were significant risk factors for reconstruction failure (Table 4).

Discussion

We evaluated the reconstruction outcomes for a cohort of 51 women who underwent mastectomy, tissue expander-based IBR, and post-mastectomy IMPT and compared the outcomes with non-irradiated contralateral reconstructions in those with bilateral mastectomies with reconstruction. Consistent with prior dosimet-

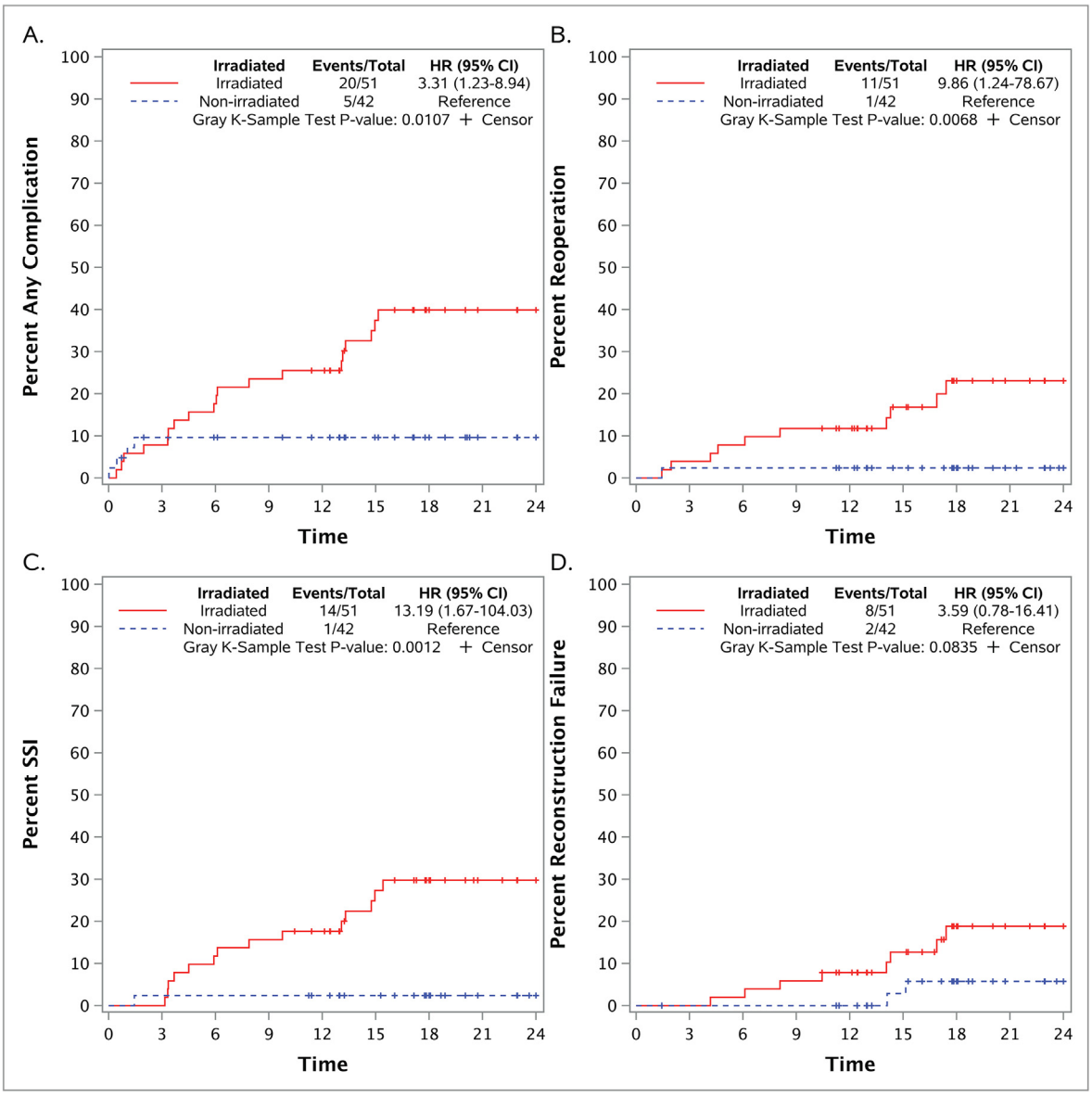

Fig. 3. Cumulative incidence of any complication (A), unplanned reoperation (B), SSI (C), and reconstruction failure (D) for irradiated and non-irradiated breasts.

ric studies, the normal tissue sparing of IMPT was exceptional without compromising target coverage, including the IMNs. Acute treatment tolerance was favorable with a 4% rate of grade 3+ skin toxicity at the end of treatment. However, similar to after photon irradiation, radiation-related reconstruction complications remain a significant source of morbidity in patients treated with IMPT.

Reconstruction failure has occurred in 16% of irradiated breasts in our study to date. As is observed after photon therapy, there was significantly more reconstruction complications in reconstructed breasts irradiated with IMPT compared with the non-irradiated contralateral reconstructed side. However, complication rates overall following IMPT compared favorably with published rates following photon therapy [18]. For example, Fowble et al. reported a reconstruction failure rate of 18% in patients treated with photon therapy, with 94% of the failures due to infection [18]. In a systematic review of complications of implant-based reconstruction, the rate of reconstruction failure was 20% for patients irradiated post reconstruction [42].

Interestingly, in our study, hypofractionation was significantly associated with SSI, unplanned reoperation, and reconstruction failure following IMPT. The higher rate of these complications was a surprising finding given that patients treated with hypofractionated photon whole breast irradiation for early stage breast cancer have been reported to have less acute and late adverse effects [43,44]. We could not perform a multivariate analysis due to the small number of events but there was no significant difference in patient age, the only other predictor of reconstruction failure, between patients treated with conventional fractionation or hypofractionation (data not shown). In the recently published phase II trial of hypofractionated photon post-mastectomy radiation by Khan et al., the total rate of implant loss or failure was 24% [45]. Results from that phase II study have formed the basis for Alliance 221505, a phase III prospective randomized trial assessing the impact on recurrence of conventional versus hypofractionated PMRT in women with reconstructed breasts, which is currently ongoing. This study will shed important insight into the role of hypofractionation in women with IBR treated with photon PMRT. Although the relative biological effectiveness (RBE) of proton therapy generally decreases with larger fraction sizes, it is possible that RBE heterogeneity of breast cancer proton ther-

Table 4
Univariate analysis of risk factors for reconstruction failure in irradiated breasts.

Variable	*P* value	Hazard ratio (95% confidence interval)
Age, per 1 year	0.002	1.14 (1.05–1.24)
Body mass index, per 1 kg/m^2	0.13	1.08 (0.98–1.18)
Smoking history, per pack-year	0.53	0.97 (0.87–1.08)
Diabetes, type II	0.97	1.05 (0.05–22.01)
Hypertension	0.95	0.94 (0.11–8.12)
Hyperlipidemia	0.56	1.57 (0.35–7.03)
Coronary artery disease	0.54	2.64 (0.12–56.94)
Clinical stage	0.43	
Stage I		1.0 (reference)
Stage II	0.53	0.57 (0.10–3.28)
Stage III	0.20	0.26(0.03–2.07)
Hormonal receptor status		
ER positive	0.34	2.73 (0.34–21.65)
PR positive	0.39	2.45 (0.31–19.25)
HER2 status		
HER2 positive	0.36	2.73 (0.32–23.48)
Number of nodes removed, per 1	0.82	1.01 (0.95–1.07)
Hypofractionation	0.024	4.99 (1.24–20.05)
CTV D0.01 cc, per 1%	0.17	0.87 (0.72–1.06)
Nodal boost	0.81	0.77 (0.09–6.47)
Expander location		
Prepectoral		1.0 (reference)
Subpectoral	0.64	1.46 (0.29–7.34)
Mastectomy type	0.83	
Skin Sparing		1.0 (reference)
Areola Sparing	0.996	0.99 (0.04–24.14)
Nipple Sparing	0.56	1.52 (0.37–6.21)
Acute radiation dermatitis grade		
Grade 1		1.0 (reference)
Grade 2/3	0.94	0.95 (0.23–3.88)

CTV = clinical target volume. ER = estrogen receptor. PR = progesterone receptor. HER2 = human epidermal growth factor receptor 2.

apy plans could have a greater effect on reconstruction in patients treated with hypofractionation [46]. Caution may be warranted when extrapolating new fractionation regimens to proton therapy based on photon experiences alone. That said, the number of patients treated with hypofractionation in our study is small and the finding of increased complications with hypofractionated versus conventionally fractionated proton therapy should be considered hypothesis generating. Of note, we recently completed accrual to MC1631, a randomized phase II trial of 15 vs 25 fraction pencil-beam scanning proton radiotherapy after mastectomy in patients requiring regional nodal irradiation. Approximately two thirds of patients on that trial underwent IBR. Therefore, the results of MC1631 will provide more robust insight into the role of hypofractionated proton PMRT in women with IBR.

Despite treatment planning efforts to limit hot-spots on the skin surface which limited the risk of severe radiation dermatitis, reconstruction complications remained a clinically significant problem in patients treated with IMPT. Further investigation is needed to identify strategies to reduce complications and implant loss after both photon and proton therapy. IMPT did offer a dramatic reduction in radiation exposure to the underlying heart and lungs in our study. A linear correlation between mean heart dose and risk for major coronary events has previously been observed, and since validated in large population-based studies [19,47]. Recently, in an analysis from the Early Breast Cancer Trialists Collaborative Group, mean lung dose was also shown to significantly correlate with death from lung cancer, the absolute risk of which was particularly pronounced in current and former smokers [20]. Here, the majority of patients treated had left-sided disease and the mean heart dose was just 0.6 Gy. Furthermore, the ipsilateral lung V20 Gy, a commonly used measure of plan quality in the breast cancer literature, was just 14%. These are marked reductions compared to recent photon reports. For comparison, target mean heart and V20 Gy constraints in the ongoing NSABP B-51/RTOG 1304 study are 4 Gy and 30%, respectively [48]. Furthermore, these reductions in dose to the heart and lungs were achieved without compromising target coverage of the regional lymphatics, which is important in order to optimize disease control [21,49,50]. Of note, the rates of grade 1 (6%) and grade 2 (2%) acute esophagitis in our series compared favorably with acute toxicities reported in other proton PMRT series. For instance, Luo et al. reported grade 1 and 2 acute esophagitis in 33% and 17% of patients, respectively. Similarly, Verma et al. reported grade 1 and 2 acute esophagitis in 31% and 33%, respectively [51,52]. Our results were likely achieved by limiting the medial extent of the supraclavicular CTV to the lateral border of the internal carotid artery, given that paratracheal and paraesophageal nodal presentations and recurrences are extremely uncommon in breast cancer, and application of a strict esophageal constraint [33–35]. To definitely establish whether the favorable dosimetry will ultimately reduce late cardiopulmonary, secondary malignancy, or recurrence events will require additional investigation of hundreds of patients and years, if not decades of close follow-up.

Potential limitations of this study include the relatively small patient numbers and that this is a single institution experience. That said, women were treated in a similar fashion, with homogeneous RT dose and treatment techniques. Further investigation is needed to determine long-term esthetic outcomes and quality of life in this patient population and whether similar outcomes can be achieved with other techniques such as passively scattered proton therapy. Overall, our results suggest that IMPT is a viable and attractive treatment option for women with IBR and indications for PMRT.

In summary, post-mastectomy IMPT following mastectomy with immediate tissue expander based breast reconstruction provides exceptional normal tissue sparing and target coverage and is associated with favorable acute toxicity. Reconstruction complications are more common in breasts irradiated with IMPT compared with non-irradiated controls; however, outcomes compare favorably with prior photon experiences. Unexpectedly, hypofractionation was associated with higher rates of reconstruction complication and failure. Therefore, further investigation of optimal dose-fractionation for both photon and proton irradiations after IBR is needed.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.022.

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