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Radiation Modality (Proton/Photon), Timing and Complication Rates in Breast Cancer Patients Receiving Two-Stage Expander/ Implant Reconstruction

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Abstract

Purpose: To explore the effect of postmastectomy radiation (PMRT) modality and timing on complication rates in patients receiving immediate Two-Stage Expander/Implant (TE/I) reconstruction implant.

Methodology: We reviewed the charts of 661 patients who underwent immediate TE/I with/ without (PMRT) at our institution from 2000–2019. Patients were divided into 3 cohorts: No radiation (NR), PMRT to expanders (RTE) and PMRT to Implants after expander exchange (RTI). PMRT was delivered either with 3D conformal photon with/without chest-wall-boost (CWB) or proton therapy. Reconstruction complications were defined as infection/necrosis requiring debridement; capsular-contracture requiring capsulotomy and reconstruction failure requiring prothesis removal. Logistic regression and Cox models were used to assess the impact of different RT modalities on complication rates and local control.

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Conflict of interest:

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Data Sharing Statement: All data generated and analyzed during this study are kept in secure RedCap database within Massachusetts General Hospital Radiation Oncology department. This data is not available for sharing under the institutional review board regulations.

Results: Among 661 patients, 309 (46.7%) received PMRT, 220/309 (71.2%) received RTE before exchange and 89/309 (28.8%) received RTI after exchange. 17/309 (5.5%) patients received proton therapy. The complications proportions among RTE vs RTI cohorts were 22.7% vs 15.7% for infection/necrosis, 13.6% vs 19.1% for capsular-contracture and 39.5% vs 31.5% for overall-reconstruction-failure, respectively. Among Proton patients, 8/17 (47%) developed capsular-contracture compared to 16.4% (24/146) and 10.3% (15/146) in CWB and NO CWB groups, respectively.

Adjusted multivariable analysis showed no significant difference between RTI and RTE in terms of infection/necrosis and capsular-contracture. Yet, RTE significantly increased overall-reconstruction-failure compared to RTI (39.5% vs 31.5%; OR 2.11; p=0.02). Protons significantly increased capsular-contracture compared to both CWB and NO CWB groups (OR: 5.4, p=0.01; and OR:10.9 p<0.001), respectively. Moreover, proton significantly increased overall-reconstruction-failure. The 5 years local control rates were 95.3% and 97.7% for RTE and RTI, respectively (HR:1.2, p=0.7).

Conclusion: Early radiation to the expander before the exchange to implant significantly increased overall reconstruction failure without improving local control. Protons significantly increased capsular contracture rates and overall reconstruction failure leading to more revision surgeries.

Introduction:

Two stages Expanders/Implant (TE/I) is a common breast reconstruction approach for patients undergoing mastectomy[1]. In a recent national survey, almost 75% of plastic surgeons in the US are using Immediate (TE/I) for their patients[2]. Moreover, other national analyses showed increased rates of postmastectomy radiation (PMRT) in the settings of (TE/I)[3]. Despite the frequency of the approach, there remains residual challenges with the optimal integration of PMRT and TE/PI. While PMRT improves tumor control for selected patients, it has been demonstrated that it increases reconstruction complications with immediate (TE/I)[4, 5]. Therefore, mitigating the impact of PMRT complications in the setting of TE/PI remains an unmet clinical need [6].

From a surgical prospective, radiation to the tissue expanders (RTE) before the exchange allows the surgeon to correct any radiation induced complications during the second surgery[7]. However, operating on irradiated tissues can be very challenging making some surgeons preferring performing the expander exchange to the permanent implant before post-mastectomy radiation starts[8, 9]. From a radiation oncology standpoint, RTE can be faced with dosimetric challenges such as increased radiation to the contralateral breast and questionable increase in the mean dose to the heart and lung [10–14]. Nevertheless, Radiation Oncologists are also concerned with delaying PMRT which might increase the risk of local failure[15].

While other studies examined this topic, the lack of universal objective definition of reconstruction complications led to wide variation in endpoints between these studies[8, 16–24]. Additionally, those studies didn’t take into account different radiation details as usage of chest wall boost (CWB) or proton irradiation into their statistical analysis nor the

difference of local control between RTI and RTE. Consequently, with such wide variation between different studies, lack of specific radiation details and the pros and cons with RTI and RTE, no clear guidelines for these clinical scenarios are available.

The goal of this study is to evaluate the impact of PMRT timing in relation to the expander exchange surgery and PMRT type on reconstruction complications as well as local control for breast cancer patients treated with immediate TE/I.

Materials and Methods:

After IRB approval, we reviewed all breast-cancer patients' charts treated with mastectomy and any reconstruction type at our institution from 2000 to 2019 (N=1,817). Only patients having their primary tumor treated with mastectomy and immediate two stages (TE/I) reconstruction were included. The following criteria were excluded: bilateral breast cancer, inflammatory breast cancer, local failure cases treated with mastectomy and reconstruction, patients who received radiation after lumpectomy and electively underwent mastectomy with reconstruction as well as patients who underwent direct-to-implant immediate reconstruction. These exclusions are rationalized that radiation naïve tissue would heal differently than irradiated tissues. Applying those criteria yielded 661 patients who were available for this analysis. All data has been stored in REDCap database within the Department of Radiation Oncology [25].

Radiation and reconstruction techniques:

All patients had the expanders placed immediately at the time of mastectomy. No patient among this series had muscle sparing/pre-pectoral placement of the expander. Usually a muscular pocket formed of the pectoralis ± serratus muscle was created to cover the expander/implant. In certain cases, depending on the plastic surgeon assessment; the expander/implant was placed partially under the pectoralis muscle with Alloderm support of the lower pole of the expander/implant. Other types of mesh as FlexHd, Vicryl, or Surginmed were used but not as frequent as Alloderm. There was no institutional guidelines nor algorithms for PMRT timing and the radiation to expanders (RTE) before exchange surgery or to the permanent implant (RTI) after the exchange. This was case by case and at the discretion of the treating physician.

PMRT was delivered using 3D-conformal external-beam 6 MV photons (opposed tangents). All patients received conventional fractionation to a median dose of 50–50.4 GY in 25–28 fractions. Chest wall boost (CWB) was delivered per physician discretion in case of positive margins or lymphovascular invasion (LVI) with 10 Gy/5 fractions en-face electrons[26]. For patients receiving photons, a 3–5 mm skin bolus was used every other day whenever adequate skin dose coverage was needed. All target volumes and organs at risk were contoured based on RTOG atlas or RADCOMP atlas based on the extent of the axillary disease and at the discretion of the treating physicians. Among the patients receiving radiation, 17 received protons using pencil beam scanning. The target volumes for protons patients were delineated according to RADCOMP atlas.

Complications definition:

In accordance to previous series[26–30], and in order to avoid inter-rater assessment variability achieving objective assessment, complications endpoints were defined based only on surgical reintervention notes. These included: infection/skin necrosis (I/N) was reported only in cases requiring surgical intervention and debridement. Capsular contracture was defined based only on revision surgery for capsulotomy or capsulectomy. Capsulotomies performed during expander-exchange to permanent implant were not counted as an event as capsulotomy during exchange is normally done to allow the exchange regardless of capsular contracture status. The modified Baker grading scale was not used in evaluating contracture, given its inter-rater variability[31]. Acknowledging the lack of universal definition for reconstruction failure, we defined it in two ways; 1) absolute reconstruction failure and 2) overall reconstruction failure. Absolute reconstruction failure is defined as permanent removal of the expander or the implant without replacement or salvage reconstruction. Overall reconstruction failure was defined as removal of the permanent implant for any complication irrespective of replacement outcomes (i.e. with and without salvage reconstruction).

Statistical Analysis:

Descriptive statistics of sample characteristics by group (RTE, RTI, and No PMRT) and complication rates by group and by radiation type were reported. Kaplan-Meier plots and 5-year cumulative incidence rates were computed for each outcome by group. An unadjusted Cox proportional hazards regression model was used to analyze the risk of local failure by group RTE vs. RTI. Only an unadjusted model was performed for local failure due to the small number of outcome events available. Multivariable logistic regression was used for each complication outcome in the full study cohort, assessing the odds of each outcome by group (reference group: No PMRT), and within the PMRT subgroup assessing RTE vs. RTI. Covariates in the multivariable models were pre-specified based on clinical knowledge/experience and prior publications, and the number of covariates included in each model varied depending on the number of outcome events available for each complication. Hypothesis tests were two-sided, and the significance threshold was set to 0.05. Statistical analyses were performed using SAS version 9.4.

Results:

Demographics:

Among 661 patients, 352 did not receive PMRT. Among the 309 who received PMRT, 220 received RTE and 89 received RTI. Additionally, 146/309 (47.2%) did not receive CWB, 146/309 (47.2%) received CWB and 17/309 (5.5%) received PMRT using protons beam to the chest wall and regional lymph nodes. Skin bolus (3–5 mm every other day in photon settings only) was used in 71.3% and 67.4% in both RTE and RTI groups, respectively (Table 1). Over 80% of patients in both RTE and RTI groups received regional nodal radiation covering axillary levels II, III and supraclavicular lymph nodes. All protons patients had these lymph nodes covered. Median follow-up from diagnosis date for the entire cohort was 7.2 (4.1–10.5) years. Patients receiving radiation had more advanced disease

in terms of staging and required more chemotherapy compared to those without PMRT (Table1). Patients receiving adjuvant chemotherapy were well balanced between RTI and RTE groups. The majority of the entire cohort (60%) had complete muscular coverage across the three groups. However, partial Alloderm support was used more often in PMRT patients; where 40.1% and 41.0% in RTE and RTI, respectively, had Alloderm support compared to 23.9% in NO-PMRT group (Table 1). No pre-pectoral or muscle sparing technique were used in this study.

Complications Rates and Local Control

The RTI and RTE had higher percentages of complications compared to NO-PMRT group. The frequency of each complication among different groups is shown in (Table2). The proportions of patients suffering from expander/implant rupture were at most 5% across the three groups (Table 2). Expander/Implant exposure rates were 7.7% in RTE group and 1.1% in RTI and No PMRT groups.

Among the radiation subgroups, infection or necrosis was the earliest complications to be reported and capsular contracture was the latest. The median time to develop infection/necrosis was 4.7 months (IQR 0.9–11.5), while capsular contracture was reported after a median time of 22.8 months (IQR 15.3–36.5). However, overall reconstruction failure happened after a median time of 13.4 months (IQR 7.7–24.8).

Skin bolus was not associated with any reconstruction complication (supplementary table 1). Chest wall boost (CWB) has been demonstrated to be a risk factor for reconstruction complications[26]. Therefore, we compared patients receiving protons to those with and without CWB to explore the difference in different PMRT modalities on complications. Bolus usage was not associated with any reconstruction complication

Strikingly, among Proton patients 47% developed capsular contracture requiring surgical intervention compared to 16.4% and 10.3% in CWB and NO-CWB groups, respectively (Proton vs. NO-CWB: OR 7.77, 95% CI 2.61–23.1, p=0.0002; CWB vs. NO-CWB: OR 1.72, 95% CI 0.86–3.43, p=0.12). Also, 52.9%, 41.8% and 30.8% suffered from overall reconstruction failure in proton, photons+CWB and photons only groups, respectively. On the other hand, no patients in proton group suffered from expander/implant exposure or rupture and leakage, and only 2 patients suffered from infection necrosis (Table 2).

Acknowledging the different follow-up time between groups, we conducted a survival analysis to account for such differences (Figure 1). The 5-year cumulative incidence rates for overall complications were 45.1%, 39.4% and 24.4% for RTE, RTI and NO-PMRT, respectively. The 5 years incidence rates for infection/necrosis, capsular contracture, absolute and overall reconstruction failures are displayed in figure 1. The 5 years local control rates were 95.3% and 97.7% for RTE and RTI, respectively (HR:1.2, p=0.7) (Figure 1E).

Multivariable analysis:

A multivariable analysis, controlling for different risk factors was performed. This included, expander/implant coverage, smoking, and BMI, and compared RTI and RTE to no PMRT

(Table 3). RTE was significantly associated with infection necrosis (OR:2.17, 95%CI: 1.35–3.47, p=0.001), capsular contracture (OR:3.40, 95% CI:1.77–6.54, p=0.0002), absolute failure (OR:2.55, 95%CI :1.18–5.52, p=0.02) and overall failure (OR:2.72, 95% CI: 1.82–4.05, p<0.0001), when compared to NO PMRT. On the other hand, RTI compared to NO-PMRT, showed significant association with contracture (OR: 5.22, 95% CI: 2.40–11.4, p<0.0001), absolute failure (OR:2.93, 95%CI:1.13–7.60, p=0.03) and overall failure (OR:1.76, 95%CI:1.00–3.10, p=0.0495). Interestingly, RTI had higher odds of infection/necrosis compared to NO-PMRT (OR:1.38, 95%CI:0.69–2.76, p=0.37), but the confidence interval was too wide to rule out the possibility of no effect. Moreover, there was no statistically significant difference in rupture or leakage when comparing RTE and RTI to NO-PMRT (Table3). There were significantly higher odds of implant/expander exposure in RTE compared to NO-PMRT (OR:7.34, 95%CI: 2.41–22.3, p=0.0004) but not between RTI and NO-PMRT (OR:1.03, 95%CI:0.11–9.45, p=0.98). Active smoker was found to be significantly associated with infection and overall failure; while complete or partial muscular coverage without ADM or mesh significantly increased capsular contracture and overall failure compared to partial Alloderm support, consisting with previous literature and results[6].

Comparison between different Radiation cohorts

A multivariable model adjusting for different radiation types and time as well as other complications risk factors was conducted. There were no statistically significant differences between RTI and RTE in terms of infection/necrosis, capsular contracture, absolute failure, or expander/implant rupture and exposure (Table 3). However, RTE remained significantly associated with overall reconstruction failure compared to RTI (39.5% vs 31.5%; OR 2.11; p=0.02). Protons were found to be significantly associated with contracture requiring capsulotomy compared to both photons+CWB and photons without CWB groups (OR: 5.37, p=0.01; OR:10.9, p<0.001), respectively. Moreover, protons were significantly associated with overall reconstruction failure compared to both photons+CWB and photons without CWB groups (OR: 3.78, p=0.03; OR:5.64, p=0.004), respectively. Delivery of CWB significantly increased I/N when compared to photons only (OR: 2.00, p=0.03). Protons did not significantly increase risk of infection compared to photons with and without CWB. No patients receiving protons had absolute failure, expander/implant rupture and exposure.

Analysis with and without Protons

Taking in consideration the low number of proton patients and the improvement of photons delivery techniques over the years, we conducted several sensitivity analyses (Supplementary tables).

After excluding 17 protons patients, multivariable models adjusting for BMI, smoking, type of mesh used, usage of boost showed that RTE remained associated with overall reconstruction failure (OR:2.33, P=0.01). There was no significant difference between RTI and RTE in terms of infection/necrosis, capsular contracture and absolute failure (Supplementary table2). Those results coincide with the primary analysis including protons.

Considering that over the study time period (2000–2019), photon planning, its delivery techniques and imaging guidance improved constantly; we conducted an extra analysis for photons and protons patients treated over the same time period (2011–2019, N=179). We found in the same time period with comparable technologies, protons were not associated with increased risks of infection/necrosis and absolute failure (Supplementary table 3), similar to the original analysis.

In accordance to the original analysis as well; protons were found to be significantly associated with contracture requiring capsulotomy compared to both photons+CWB and photons without CWB groups (OR: 16.8, $p<0.01$; OR:11, $p<0.01$), respectively. Moreover, protons remained significantly associated with overall reconstruction failure compared to both photons+CWB and photons without CWB groups (OR: 7.9, $p<0.01$; OR:8.7, $p<0.01$), respectively

Discussion:

For patients undergoing immediate TE/I reconstruction and PMRT, timing of PMRT in relation to the exchange surgery, remains a clinical dilemma. The conflicting evidence in literature regarding this topic has led to wide variations in institutional practices. Therefore, many institutions are practicing solely either RTE or RTI and report the complications rates of their practices compared to no PMRT as a control. Few studies delved into comparing RTE and RTI head to head and their findings are summarized in (Table 5)[8, 16–20, 23, 24]. Yet, the results from these studies were conflicting. Possible explanations are lack of universal definitions in reconstructions complications, variation in PMRT techniques as usage of boost or using protons radiation, different statistical analyses (hazards ratios versus odds ratios), different follow-up times across the studies and multivariable models accounting for different risk factors.

Of note, the majority of the studies listed in table 5 had small number of patients in general and in RTI group specifically. This makes the study by Yoon [23]and Cordeiro[8] the largest in literature addressing this topic (317 and 304 total PMRT patients, respectively), followed by Nava [20]and Santosa [24](159 and 150 total PMRT patients, respectively) compared to ours (309 with PMRT).

All these large studies reported higher unadjusted rates of failure and complications in RTE group in general. However, Nava et al. did not conduct a multivariable analysis for reconstruction failure, while the Cordeiro multivariable model only controlled for laterality of surgery and type of implants excluding important reconstruction failure risk factors such as BMI, smoking and radiation details. Moreover, this multivariable analysis used No-PMRT as the reference group rather than directly comparing RTE with RTI, hindering direct conclusion between both groups in terms of reconstruction failure.

Therefore, both studies from Mastectomy Reconstruction Outcomes Consortium (MROC) – including 11 institutions- by Yoon et al. and Santosa et al. mitigate those pitfalls; as their multivariable analysis controlled for different risk factors including: ADM usage, smoking and BMI between groups. Yet, Santosa, defined reconstruction failure as explantation of the

expander/or implant without subsequent replacement corresponding to Cordeiro's definition as well as to our definition of absolute failure. On the other hand, Yoon et al. defined failure as removal of expander/or implant for any complication with and without replacement, which corresponds to Nava's definition as well as to our overall failure definition. However, the MROC studies did not provide information regarding PMRT details and techniques. Additionally, Santosa et al reported 1 year outcomes while Yoon et al reported 2-year outcomes.

In our study, we included 309 patients with a median follow-up of 86.5 months (7.2 years). Our goal was to use objective definitions of complications based on surgical re-intervention and by analyzing both endpoints of reconstruction failure as the absolute and the overall reconstruction failures. Our multivariable analysis accounted for different demographics, surgical factors and radiation factors. Similar to Santosa et al. and Yoon et al. we did not find any difference between RTE and RTI in terms of major infection and explant/or implant exposure or rupture. For reconstruction failure, similar to Santosa et al. PMRT timing in relation to the exchange did not impact the absolute reconstruction failure outcome. However, unlike Yoon et al, who concluded that timing does not impact overall failure (OR: 0.72, p=0.48), we reported that PMRT before the exchange significantly increased overall failure (OR: 2.11, p=0.02). This can be plausibly explained by the difference in follow-up time, as Yoon et al. reported the 2-year outcome, whereas our study had a median follow-up of 7.2 years. While the median time to report contracture in our data was 24.4 months (IQR 15.5–50.1), the median range reflects that this complication can still happen up to 50 months. This coincides with the points raised by Cordeiro et al. in their discussion that "*longer follow-up might increase severe capsular contracture rates*"[8]. Also, reporting survival curves in this study accounted for different follow-up times emulating what happens in real world with loss to follow-up. The survival analysis was consistent with our multivariable analysis where 5-year cumulative incidence of overall failure was 37.6% and 34.1% in RTE and RTI, respectively (HR: 2.11, p=0.02). Figure 1 depicts the 5-year incidence rates for infection/necrosis, capsular contracture, absolute and overall reconstruction failures, where RTE had usually higher complications compared to RTI except for capsular contracture.

We report the 5-year cumulative incidence of capsular contracture requiring capsulotomy or capsulectomy of 21.3% in RTI and 11.6% in RTE. These results are similar to Cordeiro et al.; the authors [8] reported grade III and IV capsular contracture in RTE patients is lower than that seen in RTI patients (15.9% and 1.22% vs. 44.6% and 6.3%, respectively). In our study, we did not use the Baker scale for capsular contracture; rather we relied on operative notes for capsulotomy as our definition. This ensures that the highest objectivity and severity is achieved, avoiding inter-rater assessment with Baker scale. In our RTI group, 19.1% suffered from that outcome vs 13.6% in RTE group. One possible explanation Cordeiro provided is that RTE patients undergo extensive capsulotomies during the exchange to implant unlike RTI patients.

A novel finding of our analysis was that proton therapy has significantly increased the odds of capsular contracture, whereas RTE compared to RTI on adjusted analysis yielded no significant risk (OR:0.91, p=0.81). Protons significantly increased the odds of Capsular

contracture compared to both photons + CWB and photons without CWB groups (OR: 5.4, p=0.01; OR:10.9, p<0.001). Although the number constituting the proton cohort was small, this strong statistical association is explained by the high number of events as 8/17 (47%) of proton patients suffered from contracture. Previous study, which included more proton patients and more single stage direct-to-implant patients (known to be associated with lower capsular contracture outcomes), revealed the same outcome [30]. This can be attributed to the physical nature of protons beams, as having a finite range may lead to accumulation of higher energy doses around the expander/implant causing contracture. Yet, The benefits of proton treatment, particularly in left-sided breast cancer patients requiring regional nodal irradiation or with challenging anatomies, must be weighed against these risks of developing capsular contracture.. Therefore, a risk vs benefit assessment should be conducted by the treating radiation oncologist. Also, counseling should be provided to the patient regarding treatment expectations. Besides, better understanding of the proton treatment and different techniques as pencil beam or scattered beams can help improve treatment outcomes. The awaited results of RADCOMP randomized trial will also provide better insights into the benefits of protons in breast settings.

We also conducted different sensitivity analyses accounting for different factors (supplementary materials. Removing protons patients from the multivariable models yielded the same results where RTE significantly increased the risk of overall reconstruction failure (OR:2.33, P=0.01). Additionally, analyzing the protons and photons treated in the same time era to account for the improved technology in photons delivery yielded the same results as protons increased risks of contracture and overall failure not infection/necrosis nor absolute failure. All the sensitivity analyses confirmed the robustness of our findings.

From a statistical point of view, the low number of proton patients led to wide confidence interval. Yet, the boundaries of the confidence intervals were far from the null value of 1 leading to a strong P value <0.01. Such finding regarding protons warrants more research in this area and methods to mitigate the impact of protons PMRT on reconstruction outcomes.

Importantly, delaying PMRT after exchange surgery did not impact the local control as the 5-year local failure rates were 4.7% and 2.3% for RTE and RTI, respectively (HR:1.2, p=0.7). The low number of local failure can explain the lack of statistical significance between groups, but in general the local recurrences rates is below 5% for patients receiving PMRT.

Our study had its limitations, the retrospective nature hindered collection of Breast Q surveys outcomes. Also, we did not conduct dosimetric analysis as timing and complications are the focus of the current study. Although, multivariable analysis mitigated the retrospective nature regarding imbalance of different risk factors between the groups, a prospective randomized trial remains necessary to answer this PMRT timing question. Universal agreement about reconstruction complication definition and assessment is highly needed to avoid the current discrepancies.

To this end, we conclude that delivering PMRT before the exchange surgery of expanders to implants can lead to increased probabilities of reoperations and surgical corrections,

and hence the overall reconstruction failure. Operating on irradiated tissues can be challenging and since early radiation delivery did not improve the local control, the decision of postponing PMRT is a valid option for desiring patients and physicians. We also conclude that proton therapy significantly increased capsular contracture risks and overall reconstruction failure. Therefore, careful risk versus benefit assessment is needed before using protons.

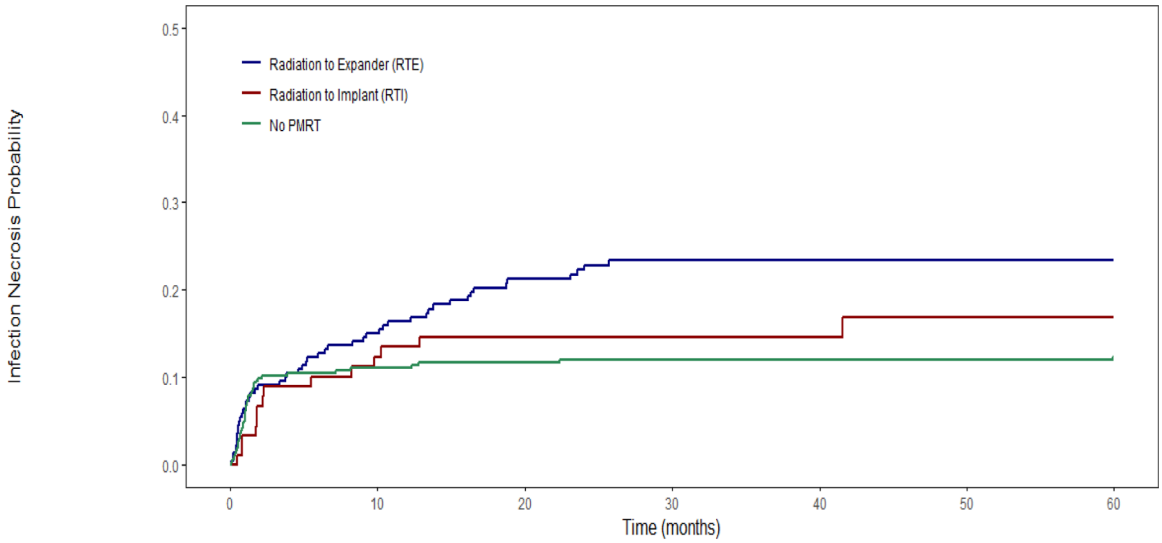
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References:

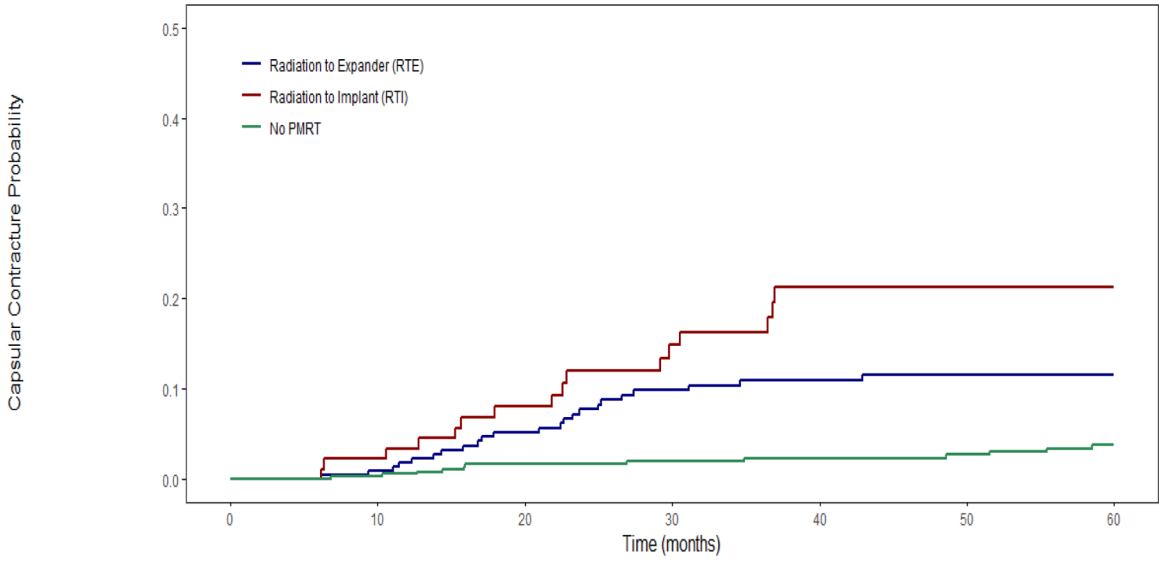
1. Panchal H and Matros E, Current Trends in Postmastectomy Breast Reconstruction. Plast Reconstr Surg, 2017. 140(5S Advances in Breast Reconstruction): p. 7s–13s.
2. Momoh AO, et al. , Postmastectomy Breast Reconstruction: Exploring Plastic Surgeon Practice Patterns and Perspectives. Plast Reconstr Surg, 2020. 145(4): p. 865–876. [PubMed: 32221191]
3. Frasier LL, et al. , Temporal Trends in Postmastectomy Radiation Therapy and Breast Reconstruction Associated With Changes in National Comprehensive Cancer Network Guidelines. JAMA Oncology, 2016. 2(1): p. 95–101. [PubMed: 26539936]
4. Jagsi R, et al. , Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst, 2018. 110(2): p. 157–65.
5. Shumway DA, et al. , Integration of Breast Reconstruction and Postmastectomy Radiotherapy. Journal of Clinical Oncology, 2020. 38(20): p. 2329–2340. [PubMed: 32442071]
6. Ho AY, et al. , Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. Lancet Oncol, 2017. 18(12): p. e742–e753. [PubMed: 29208440]
7. Kronowitz SJ, et al. , A multidisciplinary protocol for planned skin-preserving delayed breast reconstruction for patients with locally advanced breast cancer requiring postmastectomy radiation therapy: 3-year follow-up. Plast Reconstr Surg, 2011. 127(6): p. 2154–2166. [PubMed: 21311392]
8. Cordeiro PG, et al. , What Is the Optimum Timing of Postmastectomy Radiotherapy in Two-Stage Prosthetic Reconstruction: Radiation to the Tissue Expander or Permanent Implant? Plast Reconstr Surg, 2015. 135(6): p. 1509–1517. [PubMed: 25742523]
9. Cordeiro PG, et al. , Irradiation after immediate tissue expander/implant breast reconstruction: outcomes, complications, aesthetic results, and satisfaction among 156 patients. Plast Reconstr Surg, 2004. 113(3): p. 877–81. [PubMed: 15108879]
10. Farnia B, et al. , Radiation Therapy Planning and Phantom Dosimetry of a Novel Breast Tissue Expander. International Journal of Radiation Oncology, Biology, Physics, 2018. 102(3): p. e599–e600.
11. Damast S, et al. , Do metallic ports in tissue expanders affect postmastectomy radiation delivery? International Journal of Radiation Oncology, Biology, Physics, 2006. 66(1): p. 305–310. [PubMed: 16904530]
12. Suttie CF, et al. , Dosimetric Implications of Tissue Expanders in Postmastectomy Irradiation and Oncoplastic Reconstruction Outcomes. International Journal of Radiation Oncology, Biology, Physics, 2014. 90(1): p. S258.
13. Chen SA, et al. , Impact of internal metallic ports in temporary tissue expanders on postmastectomy radiation dose distribution. Int J Radiat Oncol Biol Phys, 2013. 85(3): p. 630–5. [PubMed: 22878127]
14. Kuske RR, et al. , Radiotherapy and breast reconstruction: Clinical results and dosimetry. International Journal of Radiation Oncology, Biology, Physics, 1991. 21(2): p. 339–346. [PubMed: 2061110]

15. Tsoutsou PG, et al. , Optimal timing for adjuvant radiation therapy in breast cancer: A comprehensive review and perspectives. Critical Reviews in Oncology/Hematology, 2009. 71(2): p. 102–116. [PubMed: 18922700]
16. Anderson PR, et al. , Postmastectomy chest wall radiation to a temporary tissue expander or permanent breast implant--is there a difference in complication rates? Int J Radiat Oncol Biol Phys, 2009. 74(1): p. 81–5. [PubMed: 18823714]
17. Aristei C, et al. , Expander/implant breast reconstruction before radiotherapy: outcomes in a single-institute cohort. Strahlenther Onkol, 2012. 188(12): p. 1074–9. [PubMed: 23111470]
18. Collier P, et al. , The effect of timing of postmastectomy radiation on implant-based breast reconstruction: a retrospective comparison of complication outcomes. Am J Surg, 2014. 207(3): p. 408–11; discussion 410–1. [PubMed: 24581765]
19. Fowble B, et al. , Rates of Reconstruction Failure in Patients Undergoing Immediate Reconstruction With Tissue Expanders and/or Implants and Postmastectomy Radiation Therapy. Int J Radiat Oncol Biol Phys, 2015. 92(3): p. 634–41. [PubMed: 25936815]
20. Nava MB, et al. , Outcome of different timings of radiotherapy in implant-based breast reconstructions. Plast Reconstr Surg, 2011. 128(2): p. 353–359. [PubMed: 21788827]
21. Ogita M, et al. , Risk factors for complications among breast cancer patients treated with post-mastectomy radiotherapy and immediate tissue-expander/permanent implant reconstruction: a retrospective cohort study. Breast Cancer, 2018. 25(2): p. 167–175. [PubMed: 29052108]
22. Yan C, et al. , The Timing of Breast Irradiation in Two-Stage Expander/Implant Breast Reconstruction. Breast J, 2016. 22(3): p. 322–9. [PubMed: 26864463]
23. Yoon AP, et al. , Patient-Reported Outcomes after Irradiation of Tissue Expander versus Permanent Implant in Breast Reconstruction: A Multicenter Prospective Study. Plast Reconstr Surg, 2020. 145(5): p. 917e–926e.
24. Santosa KB, et al. , Postmastectomy Radiation Therapy and Two-Stage Implant-Based Breast Reconstruction: Is There a Better Time to Irradiate? Plast Reconstr Surg, 2016. 138(4): p. 761–769. [PubMed: 27673513]
25. Harris PA, et al. , Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 2009. 42(2): p. 377–381. [PubMed: 18929686]
26. Naoum GE, et al. , 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(1): p. 155–164. [PubMed: 31055108]
27. Naoum GE, et al. , Single Stage Direct-to-Implant Breast Reconstruction Has Lower Complication Rates Than Tissue Expander and Implant and Comparable Rates to Autologous Reconstruction in Patients Receiving Postmastectomy Radiation. Int J Radiat Oncol Biol Phys, 2020. 106(3): p. 514–524. [PubMed: 31756414]
28. Naoum GE, et al. , Optimal breast reconstruction type for patients treated with neoadjuvant chemotherapy, mastectomy followed by radiation therapy. Breast Cancer Res Treat, 2020. 183(1): p. 127–136. [PubMed: 32607638]
29. Naoum GE, et al. , Machine Learning Nomogram to Predict Breast Reconstruction Complications with and without Radiation. International Journal of Radiation Oncology, Biology, Physics, 2020. 108(3): p. e20.
30. Naoum GE, et al. , Risk of Developing Breast Reconstruction Complications: A Machine-Learning Nomogram for Individualized Risk Estimation with and without Postmastectomy Radiation Therapy. Plast Reconstr Surg, 2022. 149(1): p. 1e–12e. [PubMed: 34936596]
31. de Bakker E, et al. , The Baker Classification for Capsular Contracture in Breast Implant Surgery Is Unreliable as a Diagnostic Tool. Plast Reconstr Surg, 2020. 146(5): p. 956–962. [PubMed: 32852468]



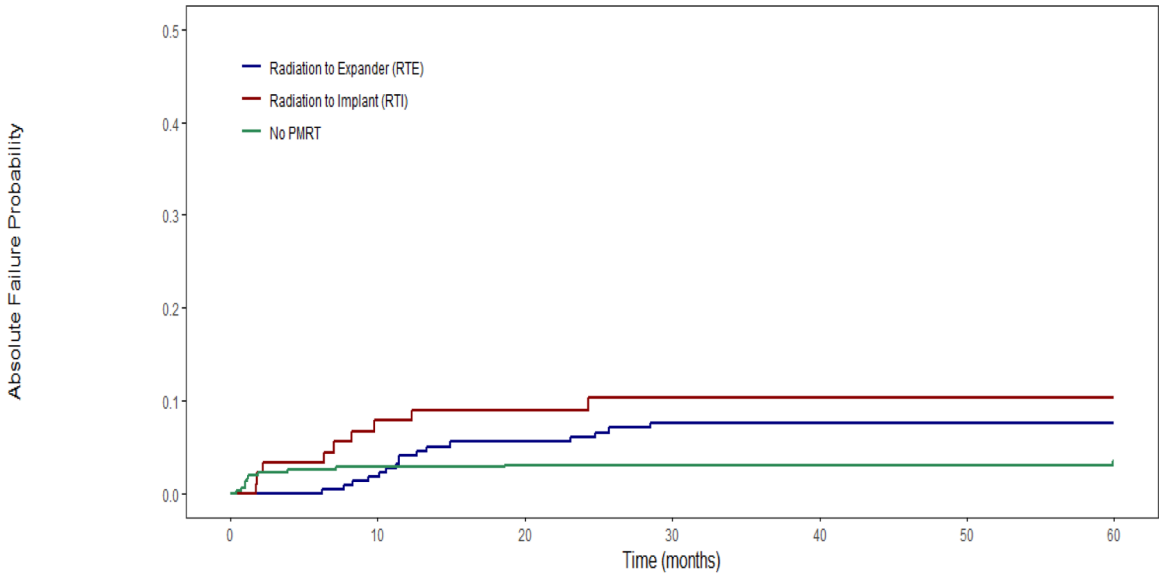
Number at risk

Radiation to Expander (RTE)	220	183	158	140	129	121	109
Radiation to Implant (RTI)	89	78	67	57	39	28	21
No PMRT	352	311	300	284	273	251	233



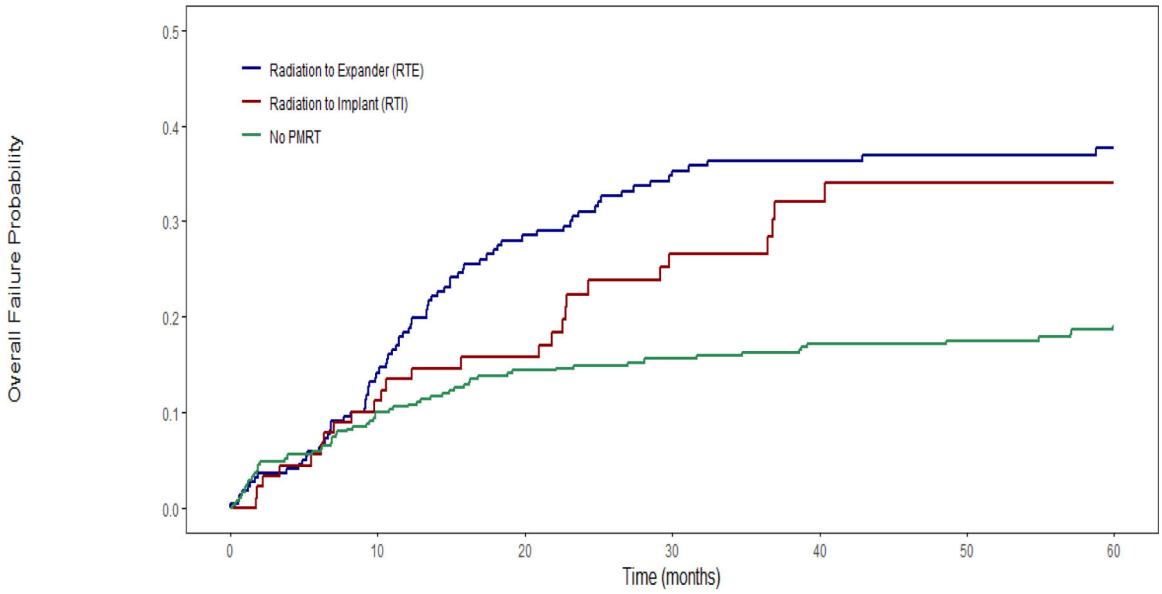
Number at risk

Radiation to Expander (RTE)	220	214	191	165	151	141	128
Radiation to Implant (RTI)	89	87	74	60	42	30	23
No PMRT	352	346	330	313	298	273	251



Number at risk

Radiation to Expander (RTE)	220	212	191	171	159	150	136
Radiation to Implant (RTI)	89	82	72	61	44	33	25
No PMRT	351	339	327	311	298	275	256



Number at risk

Radiation to Expander (RTE)	220	185	143	120	108	102	90
Radiation to Implant (RTI)	89	79	67	51	33	22	16
No PMRT	350	313	288	269	255	235	216

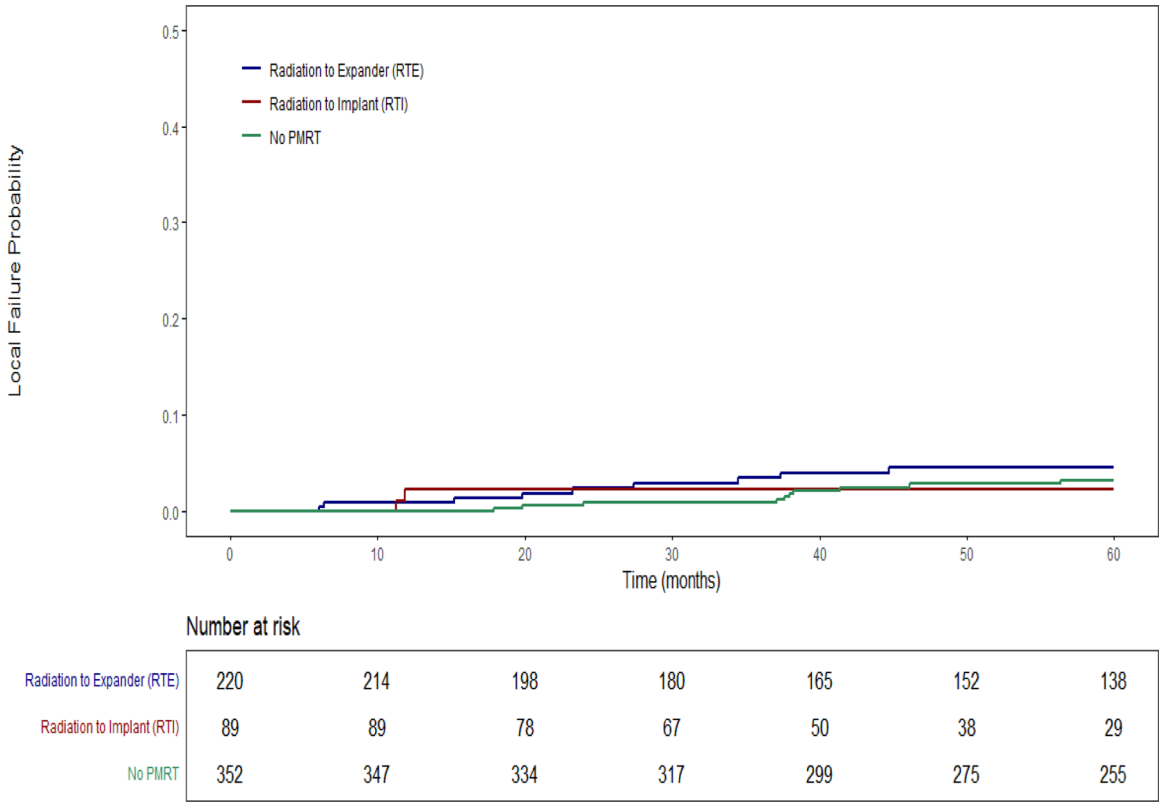


Figure 1:

A The 5-year cumulative incidence rates for infection necrosis are 23.3% for RTE, 16.9% for RTI, and 12.3% for No PMRT.

B The 5-year cumulative incidence rates for capsular contracture are 11.6% for RTE, 21.3% for RTI, and 3.8% for No PMRT.

C The 5-year cumulative incidence rates for absolute failure are 7.7% for RTE, 10.4% for RTI, and 3.5% for No PMRT.

D The 5-year cumulative incidence rates for overall failure are 37.6% for RTE, 34.1% for RTI, and 19.1% for No PMRT.

E The 5-year cumulative incidence rates for Local failure are 4.7% for RTE, 2.3% for RTI, and 3.6% for No PMRT

Table 1

Demographics and clinicopathologic features in study groups

Variable	RTE (n = 220)	RTI (n = 89)	No PMRT (n = 352)	Overall (n = 661)
Radiation				
No RT (%)	0 (0)	0 (0)	352 (100)	352 (53.3)
Proton (%)	3 (1.4)	14 (15.7)	0 (0)	17 (2.6)
RT w/ boost (%)	117 (53.2)	29 (32.6)	0 (0)	146 (22.1)
RT w/o boost (%)	100 (45.5)	46 (51.7)	0 (0)	146 (22.1)
Skin bolus (applied in photon settings only) (%)	157 (71.3)	60 (67.4)	0 (0)	217 (32.8)
Regional nodal irradiation * (%)	181 (83.4)	80 (89.9)	0 (0)	261 (39.4)
Internal mammary nodes radiation (%)	46 (20.9)	37 (41.6)	0 (0)	83 (12.5)
Mesh used				
Alloderm (%)	87 (40.1)	34 (41)	83 (23.9)	204 (31.5)
Complete muscular coverage (%)	115 (53)	36 (43.4)	238 (68.4)	389 (60)
Other mesh used (Surginmed/FlexHD) (%)	15 (6.9)	13 (15.7)	27 (7.8)	55 (8.5)
Smoking history				
Active (%)	12 (5.7)	6 (7)	29 (8.8)	47 (7.5)
Ex-smoker (%)	67 (31.8)	23 (26.7)	104 (31.5)	194 (30.9)
Nonsmoker (%)	132 (62.6)	57 (66.3)	197 (59.7)	386 (61.6)
Median age (IQR)	46.3 (40.5, 51.8)	44.1 (38.9, 49.9)	48.2 (42.5, 54.2)	47.0 (40.9, 52.8)
Median BMI (IQR)	24.4 (21.6, 28.5)	24.9 (21.8, 27.8)	23.6 (21.3, 26.7)	24.0 (21.5, 27.5)
LVI				
Negative (%)	104 (47.3)	34 (38.2)	291 (82.7)	429 (64.9)
Positive (%)	116 (52.7)	55 (61.8)	61 (17.3)	232 (35.1)
T stage				
T0** (%)	14 (6.4)	4 (4.5)	64 (18.2)	82 (12.4)
T1 (%)	76 (34.5)	31 (34.8)	231 (65.6)	338 (51.1)
T2 (%)	99 (45)	42 (47.2)	55 (15.6)	196 (29.7)
T3 (%)	29 (13.2)	12 (13.5)	2 (0.6)	43 (6.5)
T4 (%)	2 (0.9)	0 (0)	0 (0)	2 (0.3)
N stage				
0 (%)	55 (25)	25 (28.1)	319 (90.6)	399 (60.4)
1 (%)	108 (49.1)	46 (51.7)	32 (9.1)	186 (28.1)
2 (%)	38 (17.3)	14 (15.7)	1 (0.3)	53 (8)
3 (%)	19 (8.6)	4 (4.5)	0 (0)	23 (3.5)
Triple negative				
No (%)	201 (91.4)	87 (97.8)	330 (93.8)	618 (93.5)
Yes (%)	19 (8.6)	2 (2.2)	22 (6.3)	43 (6.5)
Estrogen				
Positive (%)	181 (82.3)	79 (88.8)	286 (81.3)	546 (82.6)
Negative (%)	37 (16.8)	10 (11.2)	56 (15.9)	103 (15.6)
Faintly stained (%)	0 (0)	0 (0)	3 (0.9)	3 (0.5)

Variable	RTE (n = 220)	RTI (n = 89)	No PMRT (n = 352)	Overall (n = 661)
Not done (%)	2 (0.9)	0 (0)	7 (2)	9 (1.4)
Progesterone				
Positive (%)	162 (73.6)	71 (79.8)	272 (77.3)	505 (76.4)
Negative (%)	55 (25)	17 (19.1)	69 (19.6)	141 (21.3)
Faintly stained (%)	1 (0.5)	1 (1.1)	3 (0.9)	5 (0.8)
Not done (%)	2 (0.9)	0 (0)	8 (2.3)	10 (1.5)
HER2				
Positive (%)	61 (27.7)	23 (25.8)	53 (15.1)	137 (20.7)
Negative (%)	156 (70.9)	65 (73)	227 (64.5)	448 (67.8)
Not done (%)	3 (1.4)	1 (1.1)	72 (20.5)	76 (11.5)
Chemotherapy				
No chemotherapy (%)	17 (7.7)	9 (10.1)	212 (60.2)	238 (36)
Neoadjuvant +/− adjuvant (%)	63 (28.6)	19 (21.3)	15 (4.3)	97 (14.8)
Adjuvant chemotherapy alone (%)	140 (63.6)	61 (68.5)	125 (35.9)	326 (49.6)
Median follow-up from reconstruction to last follow-up in months (IQR)	84.3 (46.6, 115.7)	45.5 (30.7, 68.5)	101.5 (58.8, 136.4)	84.0 (47.0, 123.5)
Median follow-up from diagnosis date to last follow-up in months (IQR)	86.1 (48.2, 118.4)	48.8 (32.7, 69.3)	105.5 (61.5, 138.4)	86.5 (49.7, 125.8)

Abbreviations: BMI = body mass index; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; LVI = lymphovascular invasion; PMRT = postmastectomy radiation therapy; RT = radiation therapy; RTE = radiation to expander; RTI = radiation to implant; w/ = with, w/o = without.

* Regional nodal irradiation includes covering axillary level II, III, and supraclavicular lymph nodes. Patients with T0 receiving PMRT are those who had pathological complete response (pCR) after neoadjuvant chemotherapy.

Table 2:

Complications Rate across different groups:

	Infection/Skin necrosis	Capsular Contracture	Expander/ Implant Exposure	Rupture or Leakage	Absolute Failure	Overall Failure
Group						
Radiation to Expander (RTE) (N=220)	50 (22.7%)	30 (13.6%)	17 (7.7%)	11 (5.0%)	19 (8.6%)	87 (39.5%)
Radiation to Implant (RTI) (N=89)	14 (15.7%)	17 (19.1%)	1 (1.1%)	2 (2.2%)	9 (10.1%)	28 (31.5%)
No PMRT (N=352)	45 (12.8%)	17 (4.8%)	4 (1.1%)	16 (4.5%)	13 (3.7%)	77 (21.9%)
Radiation Type						
Protons (N=17)	2 (11.8%)	8 (47%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (52.9%)
Photons + Chest Wall (CWB) (N=146)	42 (28.8%)	24 (16.4%)	14 (9.6%)	8 (5.5%)	20 (13.7%)	61 (41.8%)
Photons Without Chest Wall (CWB) (N=146)	20 (13.7%)	15 (10.3%)	4 (2.7%)	5 (3.4%)	8 (5.5%)	45 (30.8%)

PMRT = post-mastectomy radiation therapy, CWB = chest wall boost

Table 3:

Full Study Cohort Model Analysis

	Infection/Skin Necrosis (OR [95% CI], P value)	Capsular Contracture (OR [95% CI], P value)	Expander/ Implant Exposure (OR [95% CI], P value)	Rupture or Leakage (OR [95% CI], P value)	Absolute Failure (OR [95% CI], P value)	Overall Failure (OR [95% CI], P value)
Radiation to Expander (RTE) vs No PMRT	2.17 [1.35–3.47], p=0.001	3.40 [1.77–6.54], p=0.0002	7.34 [2.41–22.3], p=0.0004	1.30 [0.57–2.97], p=0.53	2.55 [1.18–5.52], p=0.02	2.72 [1.82–4.05], p<0.0001
Radiation to Implant (RTI) vs No PMRT	1.38 [0.69–2.76], p=0.37	5.22 [2.40–11.4], p<0.0001	1.03 [0.11–9.45], p=0.98	0.60 [0.13–2.74], p=0.51	2.93 [1.13–7.60], p=0.03	1.76 [1.00–3.10], p=0.0495
Complete muscular coverage vs Alloderm	1.13 [0.70–1.84], p=0.62	2.14 [1.11–4.13], p=0.02	1.01 [0.40–2.56], p=0.99	1.25 [0.52–2.98], p=0.62	1.63 [0.72–3.68], p=0.24	1.53 [1.01–2.31], p=0.04
Other Mesh used (Surginmed/ FlexHD) vs Alloderm	0.89 [0.37–2.12], p=0.79	1.08 [0.33–3.54], p=0.90	1.27 [0.25–6.36],p=0.77	0.50 [0.06–4.12], p=0.52	2.15 [0.67–6.94], p=0.20	1.14 [0.56–2.33], p=0.72
Active vs Non-smoker	3.35 [1.68–6.67], p=0.0006	0.98 [0.35–2.72], p=0.97	N/A	1.24 [0.35–4.41], p=0.74	1.70 [0.60–4.81], p=0.32	2.22 [1.17–4.22], p=0.01
Ex-smoker vs Non-smoker	1.07 [0.66–1.74], p=0.79	0.64 [0.33–1.25], p=0.19	N/A	0.37 [0.13–1.11], p=0.08	0.53 [0.22–1.27], p=0.16	0.78 [0.51–1.17], p=0.23
BMI	1.04, [1.00–1.08], p=0.06	0.99 [0.93–1.04], p=0.61	N/A	N/A	1.02 [0.96–1.08], p=0.53	1.02 [0.99–1.06], p=0.17

OR = odds ratio, CI = confidence interval, PMRT = post-mastectomy radiation therapy, BMI = body mass index

Table 4:

Subgroup Analysis For PMRT Patients Only.

	Infection/Skin Necrosis (OR [95% CI], P value)	Capsular Contracture (OR [95% CI], P value)	Expander/ Implant Exposure (OR [95% CI], P value)	Rupture or Leakage (OR [95% CI], P value)	Absolute Failure (OR [95% CI], P value)	Overall Failure (OR [95% CI], P value)
Radiation to Expander (RTE) vs Radiation to Implant (RTI)	1.55 [0.74–3.27], p=0.25	0.91 [0.40–2.04], p=0.81	5.38 [0.70–41.4], p=0.11	1.83 [0.39–8.52], p=0.44	0.59 [0.25–1.41], p=0.24	2.11 [1.11–4.02], p=0.02
Protons vs Photons Only	1.34 [0.26–6.91], p=0.73	10.9 [2.87–41.6], p=0.0004	N/A	N/A	N/A	5.64 [1.72–18.5], p=0.004
Protons vs (Photons + CWB)	0.67 [0.13–3.39], p=0.63	5.37 [1.47–19.6], p=0.01	N/A	N/A	N/A	3.78 [1.16–12.4], p=0.03
(Photons+CWB) vs Photons Only	2.00 [1.06–3.77], p=0.03	2.04 [0.94–4.41], p=0.08	3.37 [1.07–10.6], p=0.04	1.54 [0.49–4.86], p=0.46	2.94 [1.24–7.01], p=0.01	1.56 [0.90–2.70], p=0.11
Complete muscular coverage vs Alloderm	0.86 [0.46–1.61], p=0.63	2.72 [1.22–6.06], p=0.01	N/A	N/A	N/A	1.56 [0.90–2.70], p=0.11
Other Mesh used (Surginmed/FlexHD) vs Alloderm	1.06 [0.35–3.25], p=0.91	2.66 [0.71–9.97], p=0.15	N/A	N/A	N/A	2.92[1.13–7.57], p=0.03
Active vs Non-smoker	4.48 [1.56–12.9], p=0.005	0.86 [0.22–3.33], p=0.82	N/A	N/A	N/A	3.73 [1.27–11.0], p=0.02
Ex-smoker vs Non-smoker	0.90 [0.46–1.76], p=0.77	0.69 [0.31–1.54], p=0.37	N/A	N/A	N/A	0.73 [0.41–1.30], p=0.29
BMI	1.06 [1.01–1.12], p=0.02	1.01 [0.95–1.08], p=0.76	N/A	N/A	N/A	1.07 [1.02–1.12], p=0.004

OR = odds ratio, CI = confidence interval, PMRT = post-mastectomy radiation therapy, CWB =, chest wall boost, BMI = body mass index

Table 5:

Literature Review

Study	Total Patients Receiving PMRT	Total Patients in each group		Reconstructive failure Crude Rates**		5 years incidence Reconstruct Failure		Median follow-up for the entire cohort in Months	Analysis Adjusted for Radiation details and Reconstruction details
		RT to TE	RT to PI	RT to TE	RT to PI	RT to TE	RT to PI		
Collier (2014)	54	32	22	2 (6.2%)	1 (4.5%)	N/A	N/A	N/a	No
Anderson(2009)	74	62	12	3 (4.8%)	0	24%	48%	48	No
Fowble (2016)	99	86	13	17 (19.7%)	1 (7.6%)	N/A	N/A	45.6	Yes
Ogita (2018)	81	32	49	5 (15.6%)	5 (10.2%)	16.7 %	16.7%	32	No
Aristei (2012)	101	90	11	9 (10%)	3 (27.2%)	N/A	N/A	50	No
Santosa (2016) 1 year outcomes	150	104	46	12 (11.5%)	4 (8.6%)	N/A	N/A	15.4	Yes
Nava (2011)	159	50	109	20 (40%)	7 (6.4%)	N/A	N/A	50	No
Cordeiro (2015)	304	94	210	17 (18%)	26 (12.3%)	32%	16.4%	N/A	No
Naoum (Current Study)	309	220	89	19 (8.6%)	9 (10.1%)	7.8%	10.4%	86.4	Yes
Yoon (2020) Reports only 2 years outcomes	317	237	80	47 (19.8%)	8 (10.0%)	N/A	N/A	N/A	No

RT= Radiation, TE= Tissue expander, PI= Permanent Implant.

** Different reconstruction failure definitions were used across those studies. Therefore, the comparisons between those rates should be taken with caution. Additionally, the different follow-up time between studies explains the wide variation of complications rate.

For example, Cordeiro et al defined failure as expander or implant total loss which corresponds to our absolute failure definition. While Yoon et al, defined failure as removal of implant for any complications regardless replacement which corresponds to our overall failure definition. We report in this table our absolute failure rates.