Ann Surg Oncol (2019) 26:3312–3320
https://doi.org/10.1245/s10434-019-07538-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Neoadjuvant Radiotherapy to Facilitate Immediate Breast Reconstruction: A Systematic Review and Current Clinical Trials

Puneet Singh, MD[1], Karen Hoffman, MD[2], Mark V. Schaverien, MD[3], Kate J. Krause, MS[4], Charles Butler, MD[3], Benjamin D. Smith, MD[2], and Henry M. Kuerer, MD, PhD, FACS[1]

[1]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Research Medical Library, The University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT

Background. Postmastectomy radiotherapy currently is used for locally advanced breast cancers that carry a high risk of locoregional failure. However, radiotherapy can have deleterious effects on immediate breast reconstruction (IBR). Neoadjuvant radiotherapy (NART) to facilitate postmastectomy IBR is an emerging new therapeutic sequence. A systematic review was undertaken to evaluate the current evidence on the feasibility and safety of this sequence.

Methods. A comprehensive search of MEDLINE, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov from inception to 2018 was conducted, resulting in 592 records. The review included 18 retrospective and prospective studies of NART and IBR.

Results. The majority of the studies used whole-breast radiotherapy with 50 Gy, conventionally fractionated, and waited 6–8 weeks before surgery. The IBR methods were varied, with both implant and autologous reconstructions. No intraoperative complications occurred, and the postoperative complication rates ranged from 3 to 36%. The partial and total flap loss rates were very low. Studies reporting cosmetic outcomes rated the majority of cases as good or excellent. The pathologic complete response rates ranged from 17 to 55%, and the locoregional recurrence rates were low ($\leq$ 10%), with a short follow-up period. The current MD Anderson Cancer Center prospective clinical trial is described.

Conclusions. The initial results of NART and IBR demonstrate the safety of this treatment both technically and oncologically. Longer follow-up evaluation of these studies and larger prospective controlled clinical trials are needed to establish this new therapeutic sequence as a standard of care.

Postmastectomy radiotherapy (PMRT) consensus guidelines indicate a benefit for node-positive and large or locally advanced primary breast cancers, particularly those with a high risk of locoregional failure. Use of PMRT decreases locoregional recurrences (LRRs) and improves survival.[1–3] However, integrating PMRT into the overall treatment strategy, especially with respect to breast reconstruction, remains a challenge.

Immediate breast reconstruction (IBR) offers multiple advantages including a single operation, reduced overall costs, superior cosmetic results, and improved psychosocial outcomes.[4] However, the potential negative effects of radiotherapy (RT) on the reconstruction must be considered. Implant-based reconstructions have increased rates of capsular contracture, infection, pain, impaired wound healing, and poor cosmesis with RT. Autologous breast

Presented in part at the 20th Annual American Society of Breast Surgeons Meeting, 4 May 2019 in Dallas, TX, USA.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07538-x) contains supplementary material, which is available to authorized users.

First Received: 15 March 2019;
Published Online: 24 July 2019

H. M. Kuerer, MD, PhD, FACS
e-mail: hkuerer@mdanderson.org

reconstruction subjected to RT also may have increased complications including flap contracture and volume loss, poor cosmesis, and increased fat necrosis.[1,4]

A meta-analysis by Schaverien et al. demonstrated significantly increased rates of flap fat necrosis and volume loss for patients who received PMRT compared with those who did not. Notably, most studies did not involve RT delivery to the internal mammary and infraclavicular lymph node basins.[4] Because of these difficulties, many patients are forced to undergo initial mastectomy without any reconstruction at all or to undergo staged reconstruction with placement of a tissue expander (delayed-immediate reconstruction), for which PMRT is associated with a significantly increased rate of complications, including explantation,[5,6] and for which a prolonged period is typically required to complete the reconstruction. Thus, the complex decision to perform IBR in the setting wherein PMRT is indicated requires a multidisciplinary discussion.

Neoadjuvant radiotherapy (NART) is routinely used for several other cancer types that are radiosensitive such as esophageal and rectal cancer. For rectal cancer, the use of neoadjuvant systemic therapy (NST) and RT can decrease the size of tumors, leading to sphincter-preserving operations or even to a complete pathologic response on resection.[7,8]

For breast cancer, NART has historically been used for inoperable tumors, particularly in the era before modern systemic therapy. The question remains whether the sequence of therapies for node-positive and locally advanced breast cancer can be changed for administration of RT in the neoadjuvant setting, often after NST.

To our knowledge, this is the first systematic review of the literature on NART used to facilitate immediate breast reconstruction after mastectomy. This study aimed to review the data on the feasibility and safety of this emerging new therapeutic sequence.

METHODS

Information Sources and Search Strategy

A systematic search in Ovid MEDLINE, Ovid EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov from inception to 18 December 2018 was conducted. Search structures, subject headings, and keywords were tailored to each database by a medical research librarian (K.J.K.) specializing in systematic reviews. Searches were not restricted by language or study type. We searched multiple grey literature resources for conferences, dissertations, reports, and other unpublished studies for additional relevant citations. References of the included articles also were searched manually. The search terms used can be found in the complete Ovid MEDLINE search strategy shown in Supplemental Digital Content 1. Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (see PRISMA 2009 Checklist, Supplemental Digital Content 2).

Study Selection

After the initial search, two of the principal investigators (P.S., H.M.K.) independently screened the titles and abstracts of articles to identify potentially relevant studies. Disagreements were resolved by consensus. Studies that passed the title/abstract review were retrieved for full-text review. The two investigators (P.S., H.M.K.) then independently screened the remaining full-text articles. Disagreements were resolved by consensus.

Database searching retrieved 576 unique articles for review, and an additional 16 articles were identified and retrieved by manual search. From these, 18 studies met all of the criteria for inclusion in this systematic review. The PRISMA flow diagram (Fig. 1) shows the entire review process, from the original search to the final selection of studies.

Eligibility Criteria

All trials reporting on adult patients (age $>$ 18 years) with breast cancer undergoing NART followed by mastectomy and IBR by any method were included in the review. Animal studies and case reports were excluded. Studies that did not specifically state the timing of RT, including those stating that they contained only a history of RT, did not include primary data, described the concept or protocol (i.e., review article), had a small sample ($\leq$ 10 patients), or did not include IBR were excluded. Studies with a small sample were excluded because the small cohort often was part of a larger study with primary end points unrelated to the focus of this systematic review. Linked multiple reports of the same study were excluded. Reports that described different findings from the same study were combined, and we excluded papers reporting results that had already been published.

Data Extraction

Data from the included studies were extracted independently by two investigators (P.S., H.M.K.). The variables of interest were study design, patient eligibility criteria, NST and NART protocols, and reconstructive techniques. The variables related to the perioperative period included surgical complications, cosmetic outcomes, and oncologic outcomes.

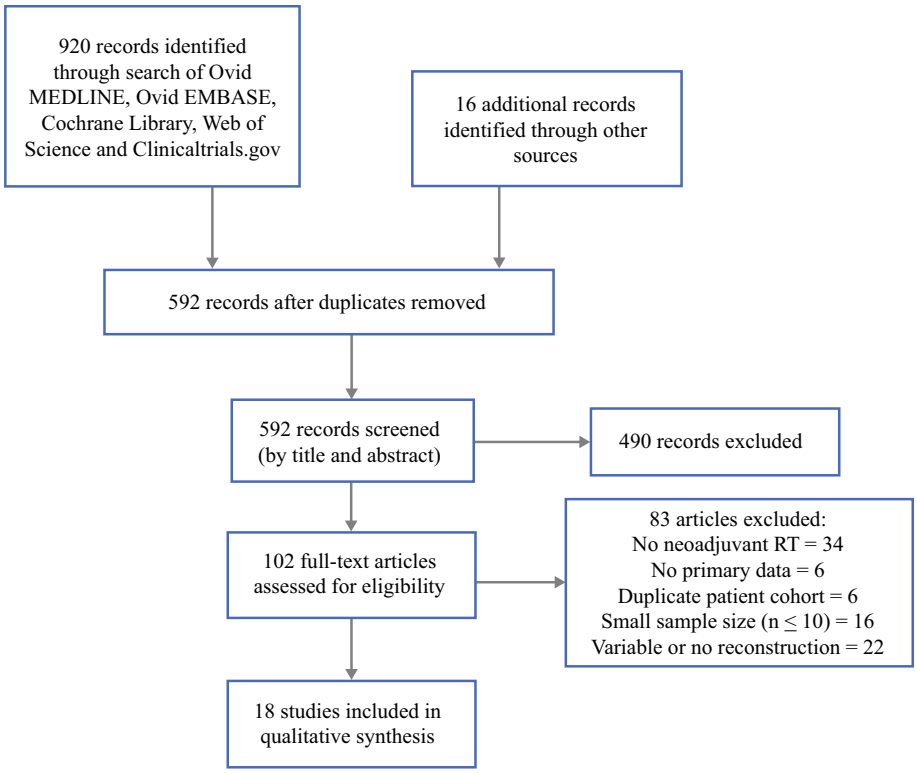

FIG. 1 PRISMA flow diagram showing selection of studies for inclusion in the systematic review

The data collected were reported individually or combined as ranges for a particular variable without any assumptions. Due to the heterogeneity of the studies, including protocol design and outcomes measured, a formal meta-analysis of the data was not possible.

RESULTS

The review identified 936 records. After removal of duplicates, 592 unique records were screened by title and abstract. Of these, 102 full-text articles were assessed for eligibility, and after exclusion of studies that did not meet the criteria, 18 studies were included for review (Fig. 1). These studies, published from 2003 to 2018, with sample sizes ranging from 16 to 210 patients, are listed in Table 1. Of these studies, 10 were performed retrospectively,[9–18] including one by Baltodano et al.[16] using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. The remaining eight trials were prospectively designed,[19–26] five of which were multicenter trials.[20–24]

Neoadjuvant Therapy

The majority of the studies reported the NART dose and the interval between completion of RT and surgery. The RT dose administered ranged from 50 to 50.4 Gy, conventionally fractionated in 11 of the studies.[10,11,13–15,17–21,23,26]

Ho et al.[18] noted that patients received either 50.4 Gy conventionally fractionated or 42.5 Gy hypofractionated (2.5 Gy per fraction during 3.5 weeks). In contrast, Thiruchelvam et al.[22] described all patients in the PRADA trial receiving hypofractionated RT, either 42.72 Gy in 16 fractions or 40 Gy in 15 fractions. Two groups also stated whether a boost was given (a dose of 6–11 Gy in the Gerlach et al.[17] study compared with a dose of 10 Gy in the Monrigal et al.[11] study). Regional RT involving supraclavicular regions was included in five studies,[14,15,18,19,21,23] whereas eight other studies radiated regional (supraclavicular and internal mammary) nodes on an individual case basis.[10,13,17,20–23,26] The RT protocol included the axilla in the Ho et al. study,[18] and another six studies stated that axillary RT was performed when indicated.[13,14,20–23]

The interval between completion of NART and surgery also differed between the studies. The oldest study included in this review reported a median interval of 16 weeks, which was noted to allow full recovery from acute radiation effects.[17] More recent studies waited approximately 6–8 weeks before performing mastectomy with IBR.[10,11,13–15,18–21,23–26] Thiruchelvam et al.[22] reported the shortest interval, a mean period of 4.4 weeks. Grinsell et al.[25] stated that a 6-week interval was chosen, based on experience with other oncologic reconstructions,

TABLE 1 Characteristics of the studies included in the systematic review

Author	Year	Type of study	Sample size (*n*)	RT protocol	Interval between NART and surgery	Type of reconstruction	Summary of complication rates and cosmetic outcomes	Summary of oncologic outcomes
Gerlach et al.[17]	2003	Retrospective, single institution	22	49–51 Gy + Boost 6–11 Gy	16 weeks (median)	Autologous (TRAM flap)	NR	Higher rates of pCR and pPR with NST/NART than NST alone; NART significant factor for achieving pCR on univariate analysis
Pinsolle et al.[9]	2006	Retrospective, single institution	42	NR	NR	Autologous (LD flap) and/or implant	Increased capsular contracture with NART; no difference in skin necrosis with or without RT	NR
Giacalone et al.[19]	2010	Prospective, single institution	26	50 Gy	8.5 weeks (mean}	Autologous (LD flap) with implant	No difference in early or late complications compared to adjuvant RT with delayed reconstruction group	16.6% pCR rate. 7.7% local recurrence rate
Monrigal et al.[11]	2011	Retrospective, single institution	210	50 Gy +/− Boost 10 Gy	6–8 weeks	Autologous (LD or TRAM flaps) and/or implant	21.9% rate of early complications, 26.2% rate of late complications	5-yr OS and DFS 86.7% and 75.6%, respectively
Ho et al.[18]	2012	Retrospective, single institution	30	50.4 Gy or 42.5 Gy (hypofractionated)	6.9 weeks (median)	Autologous (TRAM or LD flaps)	37% local complications, 66% rated as good or excellent aesthetic outcome	5-yr actuarial LRR-free survival, DRFS, DSS were 80, 65 and 68%, respectively
Paillocher et al.[10]	2016	Retrospective, single institution	111	50 Gy	5.9 weeks (median)	Autologous (LD flap) +/− implant	66.6% rate of early complications, 43.2% rate of late complications. High patient satisfaction	DFS 93.2% and OS 98.3%, median follow-up 31.6 mos
Zinzindohoué et al.[20]	2016	Prospective, multicenter	83	50 Gy (median)	6–8 weeks	Autologous (LD flap) +/− implant	6% rate of skin necrosis, no associated factors	DFS 93.2% and OS 98.3%, median follow-up 31.6 mos
Baker et al.[21] (abstract)	2017	Prospective, multicenter	59	50.4 Gy (median}	Approxim ately 6 weeks	Autologous	13.6% rate of grade 3 complications, no grade 4 or 5 complications. Cosmesis rated good to excellent	61.0% rate of significant pathologic downstaging
Baltodano et al.[16]	2017	Retrospective, database	75	NR	NR	Autologous or implant	No differences in postoperative surgical site morbidity, systemic morbidity, and overall morbidity with NART versus no NART	NR
Barrou et al.[15]	2017	Retrospective, multicenter	103	50 Gy + 46 Gy to regional nodes	6–8 weeks	Autologous (LD flap)	Overall complication rate of 9.7%. Reconstruction with implant associated with higher complication rate	53.4% pCR rate across all tumor types, higher in Her2+ and triple negative tumors
Lee et al.[12]	2017	Retrospective, single institution	18	NR	NR	Autologous or implant	No increased risk of lymphedema with NART compared to no RT	NR
Pazos et al.[13]	2017	Retrospective, single institution	22	50.4 Gy	6.7 weeks (median)	Autologous (DIEP, TRAM or LD flaps) or implant	Cosmetic result excellent or good in 66% of upfront mastectomy patients. 25% implant loss rate for wound-healing problems	55.0% pCR rate
Thiruchelvam et a1.[22] (abstract)	2017	Prospective, multicenter	19	40–42.72 Gy	4.4 weeks (mean)	Autologous (DIEP flap)	21.1% complication rate requiring reoperation; no skin necrosis or flap loss	No locoregional recurrences, 5 distant relapses and 2 breast-cancer related deaths with mean follow-up 16.2 mos
Chao et al.[24] (abstract)	2018	Prospective, multicenter	82	NR	6–7 weeks	Autologous (DIEP flap)	25% rate of any complications, 7.2% rate grade 3 complications. 1 flap necrosis and 1 skin necrosis, no flap loss	NR
Chao et al.[23] (abstract)	2018	Prospective, multicenter	62	50.4 Gy (mean)	6–7 weeks	Autologous	NR	Significant pathologic downstaging, especially for Her2+ breast cancers with 94.5% pCR rate

TABLE 1 continued

Author	Year	Type of study	Sample size (*n*)	RT protocol	Interval between NART and surgery	Type of reconstruction	Summary of complication rates and cosmetic outcomes	Summary of oncologic outcomes
Grinsell et al.[25]	2018	Prospective, single institution	29	NR	6 weeks	Autologous (DIEP or LD flaps)	3% skin necrosis and no flap loss	82.8% complete or partial response to NST/NART
Hughes et al.[14]	2018	Prospective, single institution	40	50.4 Gy	6.4 weeks (mean)	Autologous (DIEP or LD flaps)	12.5% major complication rate and 15% minor complication rate	No locoregional recurrence and 7.5% with distant recurrence
O'Halloran et al.[26]	2018	Prospective, single institution	14	50.4 Gy	7 weeks (mean)	Autologous (DIEP or LD flaps) and/or implant	No difference in complication rate compared to adjuvant RT group	Shorter time from diagnosis to completion of treatment with NART compared to adjuvant RT group ($p < 0.001$). No difference in pCR rates between the NST/NART and NST/adjuvant RT groups

NR not reported, *pCR* pathologic complete response, *pPR* pathologic partial response, *NST* neoadjuvant systemic therapy, *NART* neoadjuvant radiotherapy, *OS* overall survival, *DFS* disease-free survival, *LRR* locoregional recurrence, *DRFS* distant recurrence-free survival, *DSS* disease specific survival, *RT* radiotherapy, *mos* months

particularly reconstruction after sarcoma, as a window of time with minimal microsurgical complications. O'Halloran et al.[26] also demonstrated a significantly shorter time from diagnosis to treatment completion with NART (245.6 ± 44.2 days) compared with PMRT (291.2 ± 36.7 days; $p = 0.001$).

Because most patients recommended to receive PMRT have node-positive or locally advanced breast cancer, in the modern era, these patients also receive NST. Because these are the patients eligible for a NART trial, all prospective trials developed a treatment algorithm consisting of NST followed by NART.[19–26] In comparison, the retrospective studies included patients who received NST or adjuvant systemic therapy.[9–15,17,18] Baltodano et al.[16] did not specifically note chemotherapy status for the cohort.

Technical Factors

Reconstructive methods varied across the studies. All the studies included patients who had autologous reconstruction, and the most commonly performed flaps were transverse rectus abdominis myocutaneous (TRAM), latissimus dorsi (LD), and deep inferior epigastric perforator (DIEP) flaps.[9–26] Either DIEP or LD flaps were used in the published prospective trials.[19–23,25,26] In contrast, six studies also included patients who had implant-based reconstruction.[9,11–13,16,26] No studies reported intraoperative complications or the need to abort IBR.[9–26]

Surgical Complications

All the studies except two[7,23] reported data on complications. The commonly reported complications were seroma, hematoma, infection, skin necrosis, capsular contracture, and reconstruction failure such as flap or implant loss. Overall complications occurred in 3–36% of the cases.[13–15,22,24,26] Pinsolle et al.[9] showed that NART did not increase the risk of complications, and O'Halloran et al.[26] specifically showed no difference in complication rates between the NART and adjuvant RT groups ($p = 0.117$).

Studies using the Clavien-Dindo classification of complications demonstrated no complications greater than grade 3, which occurred in 5–15% of the cases.[21,24] Other studies divided complications into early (< 1 month) and late (> 1 month) groups. The early complications included skin necrosis, flap necrosis, hematoma, infection, and seroma, and the rates ranged from 22 to 67%. Exclusion of seromas in these trials decreased the complication rates to between 11% and 46%, indicating that seromas commonly occur.[10,11,18,19]

An interval of 7 weeks or longer between completion of NART and surgery was associated with early

complications in one study.[10] Skin necrosis was reported in 0–10% of the cases and most commonly was treated conservatively with dressing changes.[9,10,14,18,20,22,24,25] Hughes and Neoh[14] noted that all the cases of skin necrosis occurred for patients who also experienced skin necrosis on the contralateral, non-radiated side after prophylactic mastectomy with reconstruction. Thus, the authors stated that NART was unlikely to be associated with skin necrosis.

Pinsolle et al.[9] also showed no difference between the NART group and the no-RT control group. Baltodano et al.[16] used the predefined morbidity variables in the database of the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) and found a 5.3% rate of surgical-site infections (SSI), organ space SSI, wound dehiscence, and prosthesis/flap failure. The NART group and the control group (no NART) did not differ, and NART was not associated with a higher complication rate (adjusted odds ratio [OR] 1.05; 95% confidence interval [CI] 0.37–2.76; $p = 0.934$).

Late complications were observed at a rate of 26–43%.[10,11,19] Capsular contracture was frequently reported in implant-based reconstructions (with or without an autologous flap) at a rate of 15–24%.[9,19] Pinsolle et al.[9] demonstrated that NART increased the risk of capsular contracture ($p = 0.04$). However, adjuvant RT also increased the risk ($p = 5 \times 10^{-5}$). Overall, implant-based reconstruction was a risk factor for a higher complication rate in one study (OR 9; 95% CI 1.7–93; $p = 0.003$).[15] One group observed a 25% implant loss rate.[13] Autologous-only reconstructions had fewer reconstruction failures, with one case of total flap loss reported[11] and a partial flap loss rate of 3–5%.[14,18] Several studies showed no flap loss.[14,21,22,24–26]

Lymphedema, another late complication, occurred in 1–33% of the cases.[11,13] Lee et al.[12] investigated the rates of lymphedema and found no association of NART with lymphedema ($p = 0.683$).

Cosmetic Outcomes

Three groups performed aesthetic evaluations of the reconstructions. Giacalone et al.[19] used a 4-point scale for aesthetic assessment by two independent physicians and the patients themselves. Excellent-to-good results were reported in 78% of the cases by the physicians and 89% of the cases by the patients. Furthermore, compared with the control group, which had delayed breast reconstruction, there was no statistical difference in the physician ($p = 0.541$) or patient evaluations ($p = 0.723$). Pazos et al.[13] used the same scale and found that the cosmetic scores were excellent or good for 66% of the patients in the group that had mastectomy alone without a prior attempt at breast conservation. This decreased to 37% for the patients who had a previous attempt at breast conservation surgery. Similarly, Ho et al.[18] found that physician evaluation of the cosmetic outcomes was excellent or good in 66% of the cases. Paillocher et al.[10] conducted a patient satisfaction survey and found high patient satisfaction scores on average for NART and IBR, with 70% of subjects stating that they would choose the same treatment again.

Oncologic Outcomes

Pathologic complete response (pCR) rates were described in 10 studies, although the definitions of pCR varied, including use of different classification systems or non-specified definitions. The rates of pCR ranged from 16.6 to 55%.[13–15,17,19–21,23,25,26]

Gerlach et al.[17] demonstrated a significantly greater pCR rate of 42% using NART compared with 3% using PMRT ($p < 0.0001$), and NART was a significant factor for achieving pCR ($p < 0.001$) in their univariate analysis. Both groups in this study received NST.[17] In contrast, O'Halloran et al.[26] found no difference in pCR rate between the NART (37.5%) and PMRT (18.8%) groups ($p = 0.335$), with both groups receiving NST. The data are insufficient to establish a benefit of NART in addition to NST for achieving pCR. Chao et al.[23] evaluated pCR rates by tumor subtype and showed that human epidermal growth factor receptor 2-positive (HER2+) tumors had a pCR rate of 94.5% versus a 50% overall pCR rate using the Miller-Payne scoring index.

During a follow-up period of 16.2–96 months, 0–10% of patients experienced LRR.[10,11,13,14,18,19,21,22,25,26] Three prospective trials reported no LRRs during shorter mean follow-up periods of 16.2–39.8 months.[14,22,26] Distant recurrences were more common during the same follow-up period, with rates of 0–26.3%.[10,11,13,14,18,19,21,2225,26] Pazos et al.[13] reported a 2-year overall survival (OS) rate of 89.3%, a disease-free survival (DFS) rate of 79.8%, and an LRR-free survival rate of 95.2%. Two other studies reported 5-year OS rates of 86.7–98.3% and DFS rates of 71.6–93.2%.[10,11] Monrigal et al.[11] reported a 10-year OS of 75.6% and a DFS rate of 59%.

DISCUSSION

Historically, NART has been administered in the setting of inoperable breast cancer, and although some patients went on to have surgical treatment of their breast cancer, the goal of NART was not to facilitate IBR. Reconstruction, a component of treatment for breast cancer, should be

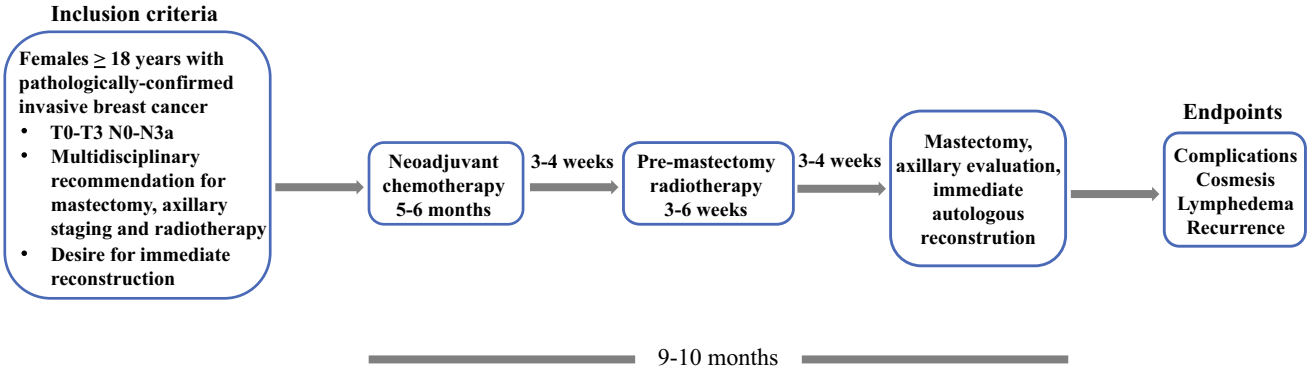

FIG. 2 MD Anderson Cancer Center neoadjuvant radiotherapy trial schema

offered to all patients. The exact timing of reconstruction is a discussion with each individual patient that should involve the input of the multidisciplinary breast team.

This systematic review aimed to evaluate the current data on NART and postmastectomy IBR and whether this treatment is safe and technically feasible. The patients eligible for these trials were those recommended to receive PMRT and those who desired immediate reconstruction. No randomized controlled trials on the subject are reported, and more recent trials are prospective in nature, with the first one published by Giacalone et al.[19] These trials in combination demonstrate that this new therapeutic sequence in node-positive and locally advanced breast cancers is safe and technically feasible. None of the included studies reported intraoperative complications with reconstruction or inability to complete reconstruction due to the irradiated field. This is consistent with experience with performing reconstructions in other irradiated fields such as after sarcoma resections or head and neck surgery.[25] Furthermore, these studies establish a safe interval between completion of NART and surgery of 6–8 weeks.

For microsurgical breast reconstruction, the condition of the internal mammary vessels is critical in determining its feasibility and safety. The initial reports of the PRADA trial demonstrate that a shorter interval of 2–4 weeks before acute radiation injury is clinically apparent may be optimal.[22]

With regard to postoperative complications, both implant- and autologous-based IBR were associated with complications. Many of the early complications were minor and often conservatively managed. Comparison of complication rates with those for control groups of adjuvant RT or no RT did not demonstrate higher rates of complications with NART, including skin necrosis and infection. The partial flap loss rates were 5% or lower, and only one of the studies reported a case of total flap loss.

The high rates of capsular contracture and implant loss in implant-based reconstructions after NART are comparable with those after PMRT.[27] Larger trials are needed to investigate whether one type of IBR may be more suitable after NART and to study the impact of different RT regimens. When reported, cosmetic outcomes were rated as good to excellent in the majority of patients.

Pathologic complete response after NST is a surrogate for prognosis, and several of the reviewed studies included this outcome. Gerlach et al.[17] noted NART to be a significant factor for achieving pCR, but older NST regimens were used. More recent studies using modern NST and NART achieved high pCR rates of 17–55%, but it cannot be determined whether these are truly associated with NART. The LRR rate was low ($\leq$ 10%), but establishing noninferiority of NART compared with PMRT will require longer follow up times and randomized controlled trials.

The MD Anderson Cancer Center multidisciplinary group has designed the first U.S.-based prospective trial of NART to facilitate IBR (NCT02912312) (Fig. 2), and has started enrolling study subjects. This trial is primarily based on the initial findings from the primary radiotherapy and DIEP flap (PRADA) pilot study that has been presented but not formally published to date.[22] In the MD Anderson trial, the NART cohort is embedded within a randomized controlled trial, and there is a planned accrual of 30 patients to demonstrate safety and feasibility. The trial aims to assess intraoperative/technical complications, postoperative complications, and oncologic outcomes for hypofractionated versus conventionally fractionated RT, and also to assess lymphedema, which is the primary aim for the randomized component of the trial.

This systematic review had some limitations. A comprehensive search strategy was used, but relevant studies may have been missed or may have yet to be formally published. We identified 16 studies via manual search, one of which was included in the final review. To increase the yield of potentially appropriate studies, the initial search also included all languages and was not restricted by year. In addition, there may have been bias in performance of the abstract and full text review for inclusion. Two reviewers performed the review to ensure that all relevant studies

were included. Because this is a relatively new concept, the studies included are likely the most robust and representative studies conducted to date.

CONCLUSIONS

Neoadjuvant radiotherapy to facilitate postmastectomy IBR is increasingly investigated in trials. The initial results from retrospective and prospective trials demonstrate its safety both technically and oncologically. However, longer follow-up evaluation of these studies in addition to larger prospective trials are needed to establish this new therapeutic sequence as a standard of care.

ACKNOWLEDGMENT This work was supported by the PH and Fay Etta Robinson Distinguished Professorship in Cancer Research (H.M.K.) and a Cancer Center Support grant from the National Institutes of Health (NIH) (CA16672).

DISCLOSURE Dr. Benjamin D. Smith has received previous grant funding from Varian Medical Systems and has current licensing/royalties from Oncora Medical. The remainder of the authors have no conflicts of interest to disclose.

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