



Management Strategies for Locally Recurrent Breast Cancer: Redo-Lumpectomy, Redo-Sentinel Node Biopsy, Redo-Radiation

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ABSTRACT A multidisciplinary approach to the management of locally recurrent breast cancer is essential. The complexities of the management of patients in this setting include discussions regarding the optimal surgical approach (breast, chest wall, and axillary surgery) and adjuvant treatment considerations (radiation/re-irradiation therapy and systemic therapy). Treatment has evolved to include the option of repeat breast conservation surgery, axillary staging, and radiation therapy through partial breast radiation techniques in selected patients.

Advances in breast cancer diagnosis and local and systemic treatments have led to improvements in patient outcomes. While the contemporary management of breast cancer has been associated with reductions in the risk of local breast cancer recurrence, unfortunately locoregional failure remains a potential risk.

The management of patients with a locoregional recurrence is complex and requires the input of a multidisciplinary team. The traditional management with salvage mastectomy (SM), axillary lymph node dissection (ALND), and adjuvant therapy has been challenged with a move towards expanding options allowing for a decrease in the extent of surgery in the breast and axilla in selected patients, offering modern techniques for re-irradiation and targeting systemic therapy by tumor subtype. This approach allows for balancing oncologic safety with risk of treatment-related morbidity.

The focus of this review is the surgical management of in-breast tumor recurrence (breast and axilla) and the role of adjuvant therapies (radiation therapy and systemic therapy) following surgery.

SURGICAL MANAGEMENT OF BREAST CANCER LOCAL RECURRENCE

Recurrence after Breast-Conserving Surgery

Local recurrence (LR) following breast-conserving surgery (BCS) presents at a later time point than that for mastectomy (median 3–4 years), with a longer interval seen in patients with hormone receptor positive disease treated with endocrine therapy.^{1–5}

A metastatic workup is indicated in the setting of management of a LR. For women who develop a LR following BCS, SM has been the standard of care.⁶ The 5- and 10-year overall survival rates following salvage mastectomy are 84% and 71% respectively.⁷ A shorter time interval to breast cancer recurrence has been shown to be associated with worse overall survival (61.9% vs. 89.3% for < 2 years vs. > 2 years).⁸

Salvage Mastectomy Salvage mastectomy with reconstruction is increasingly undertaken. There is limited literature and guidelines regarding suitability for reconstruction in this setting, and considerations include the quality of skin and tissues as well as prior adjuvant radiation therapy. Both implant and autologous reconstructions options are available for patients undergoing SM with reconstruction. Complication rates are higher following implant reconstruction compared with autologous reconstruction in this type of patient.⁹ A number of single institutional studies have demonstrated the feasibility of implant reconstruction in this

population.^{7,10–12} Complications rates following implant reconstruction are higher compared with primary mastectomy with reconstruction though aesthetic results are generally reported as “very good.” Cordeiro et al.¹⁰ reported early complication rates of 29.7% in 121 patients with a history of prior BCS and radiation compared with 15.5% ($p \leq 0.001$) in 1578 patients with no prior history of breast surgery. Flap necrosis was the most common complication (18% vs. 7.7%). Similar results were demonstrated by Lam et al., where 22 patients who underwent 33 mastectomies and immediate two-stage breast reconstructions after prior BCS and radiation were reviewed.¹¹ The overall complication rates were 27.4% at stage 1 and 19.4% at stage 2 of the procedures. No reconstruction failures were reported and revision surgery was required for 28.6% of patients.

The impact of radiation therapy on breast reconstruction failure and completion rates is important to consider in the surgical decision making process. A systematic review by Momoh et al.¹³ showed no statistically significant difference in complications rates of a cohort of patients receiving radiation before or after reconstruction.

Nipple-sparing mastectomy (NSM) could be considered for suitable patients and whose tumors do not involve the nipple areola complex. Lee et al.¹⁴ reported a study of 18 patients who had a NSM with immediate breast reconstruction for LR and compared this group with 127 patients undergoing primary NSM and reconstruction. There was no difference in complication rates encountered between the two groups except for nipple necrosis, requirement for nipple reconstruction, and need to salvage reconstruction from implant to autologous flap. When complications were analyzed by reconstruction method (implant vs. autologous), no difference between the two subgroups was noted.

Repeat Lumpectomy Repeat lumpectomy (rBCS) has emerged as a viable alternative to SM in selected patients. The oncologic safety has been demonstrated in several retrospective studies evaluating the survival outcomes of patients undergoing repeat lumpectomy compared with SM.^{15–22} In a study by Yoshida et al.²³, the impact of surgical procedure on distant disease-free survival (DDFS) and overall survival (OS) were evaluated using multivariable proportional hazards and propensity score matching. The study included 271 patients. At a median follow-up of 55 months, there was no difference in terms of DDFS and OS between the two groups, adjusted for various clinical and tumor characteristics.

The addition of radiation to rBCS is a key factor to consider. The addition of radiation has been shown to reduce the risk of a further recurrence by 18%.^{24,25} For patients with low-risk breast cancers (felt to be new primaries rather than a true recurrence), omission of radiation

therapy can be considered based on age, tumor characteristics, and tumor biology.^{26,27}

In addition to the promising data on oncologic safety of rBCS and radiation, improved cosmetic outcomes and quality of life (QoL) are other potential benefits. However, the data on these outcomes are very limited. Studies addressing cosmesis and QoL after salvage surgery suggest a better outcome in patients after rBCS compared with SM.^{28,29}

The literature to date supports the feasibility of SM with reconstruction and rBCS for patients with a breast cancer LR after prior BCS. Appropriate patient counseling regarding oncologic safety, associated complication rates, and expected cosmetic outcome is important.

Recurrence After Mastectomy

Ninety percent of local recurrences after mastectomy occur within the first 5 years of follow-up. However, later recurrences are seen in hormone positive patients treated with endocrine therapy.^{4,5} Post-mastectomy local recurrences are usually isolated and are confined to the chest wall (40–70%) but may be associated with a synchronous regional recurrence (30–40%) or occur with evidence of distant metastases at the time of recurrence diagnosis or within a few months.^{30–32} A metastatic workup is indicated in the setting of management of a LR. The major risk factors associated with post-mastectomy LR include larger tumor size and having four or more positive lymph nodes.^{33–36} In this subgroup of patients, the risk of LR is reduced with the use of adjuvant radiation therapy. Additional risk factors include younger age, hormone-negative breast cancer, and lymphovascular invasion.^{37–40} The surgical management of isolated post-mastectomy chest wall recurrences is wide local excision with negative margins. While the surgical planning for superficial recurrences is more straightforward, challenges can include disease invading the ribs, intercostal, and para-costal soft tissues. As such, factors to consider include extent of recurrence, number of nodules/sites, status of skin and flaps, depth of involvement, and local and receipt of prior radiation therapy. Reconstructive techniques may be warranted in cases of extensive disease to achieve local control and tissue coverage. In a systematic review of OS and QoL outcomes following resection of invasive chest wall disease, the 5-year OS and DFS were 40.8% and 27.1% respectively.⁴¹ Larger resections were associated with a low mortality (< 1%) and a 30-day morbidity of 20.2%.

Axillary Surgery

Axillary staging remains an integral part of breast cancer management and is important for prognostication as well as

local management. However, in comparison with the management of primary breast cancer, the recommendations in the setting of locally recurrent breast cancer are less clear. The standard of care to date has been to perform an ALND in patients who had a prior sentinel lymph node biopsy (SLNB) and no further axillary surgery for patients who have undergone a prior ALND. This dogma has been challenged with the use of SLN surgery for axillary restaging in patients with breast cancer recurrence. This procedure has been found to be associated with a high negative predictive value (NPV) and has the potential to prevent significant morbidity related to more extensive surgery.

A systematic review published by Poody et al.⁴² addressed the technical success rate, follow-up assessment, and prognostic value or repeat SLNB (rSLNB). The study included 1761 patients. Repeat SLNB was successful in 64.3% of patients (75.7% vs. 46.1%; $p < 0.0001$ with prior SLNB vs. ALND respectively), with a (NPV) of 96.5%. Identification rate and procedure success rate was higher after prior SLNB compared with ALND (77.2%, 95% confidence interval [CI] 74–80.1% vs. 56.9%, 95% CI 53.1–60.8% and 75.7%, 95% CI 72.7–78.7% vs. 46.1%, 95% CI 42.4–49.7% respectively, $p \leq 0.0001$). Aberrant drainage rate was higher after prior ALND and with a history of prior breast radiation (72.6%, 95% CI 67.9–77.3% and 70.3%, 95% CI 54.8–85.7% respectively). Positive sentinel nodes were seen in 18.2% of patients and in those who underwent completion ALND additional non-sentinel nodes metastases were found in 16.1% of patients. Regarding follow-up data, at a mean of 31.7 months, 1.30% of patients experienced a regional recurrence (of note, this data were available on 48.2% of the study cohort).

With regards to the success rate of rSLNB following prior mastectomy, studies to date have demonstrated the feasibility of the procedure with technical success rates between 69 and 100%.^{42–48} The value of this procedure in patients with prior mastectomy is in the potential to alter recommended adjuvant local and systemic therapies.

An important question arises regarding the management of the axilla after an unsuccessful rSLNB in patients with clinically node-negative disease. A recent publication by the Sentinel Node and Recurrent Breast Cancer (SNARB) study group included 239 patients with an unsuccessful rSLNB.⁴⁹ Sixty patients in the cohort underwent a further ALND, whereas only eight patients (13%) were found to have macrometastases in one or more lymph nodes. At a median follow up of 5.1 years (range 0.3–13.2), none of the patients treated with ALND experienced a regional recurrence compared with 7 patients (3.9%) in the group with no ALND after unsuccessful rSLNB. Interestingly, none of the recurrences in the study occurred in the ipsilateral axilla.

Five occurred in the contralateral axilla and one in the supraclavicular and infraclavicular region. There was no difference between the two groups in 5-year DFS (90.8% vs. 91.1%, $p = 0.980$). As such, with a low risk of regional recurrence after unsuccessful rSLNB, the study supports no further axillary surgery in patients who do not have successful mapping in this situation.

Injection of a larger amount of tracer, peritumoral and periareolar injections and using a 1-day lymphatic mapping protocol may be helpful to improve the technical success rate of these procedures.⁵⁰

ADJUVANT THERAPIES FOR THE MANAGEMENT OF BREAST CANCER LOCAL RECURRENCE

Radiation Therapy

Radiation therapy is recommended for radiation naïve patients. Radiation post mastectomy is typically administered to the chest wall and nodal basins (axillary, infraclavicular, and supraclavicular) with consideration of the internal mammary nodes. Following rBCS, whole breast irradiation (WBI) is recommended in radiation naïve patients. For patients who were treated with prior radiation therapy, the decision process is more challenging. Considerations to keep in mind include taking into account the volume of breast tissue irradiated initially to assess tissue tolerance, risk of late skin toxicity, potential cosmetic outcome, interval to recurrence (re-irradiation is not advised at an interval < 2 years), and risk of radiation to adjacent organs and in particular for left-sided tumors. However, prospective multi-institutional data has demonstrated the feasibility of re-irradiation following rBCS for patients with limited disease using partial breast techniques, including three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or intraoperative radiation for low-risk cases. For those patients who undergo rBCS and have more advanced or node-positive disease, previous treatment plans must be reviewed to ensure safety with respect to heart/lung doses as well as the brachial plexus. Radiation techniques include use of 3D-CRT or IMRT primarily.

Studies, including patients with repeat lumpectomy and no radiation, reveal recurrence rates between 4 and 50% compared with a second LR rate of 3–22% after salvage mastectomy.^{15–22} Literature to date supports treatment with radiation therapy following rBCS. This has been shown to be associated with improvement in oncologic outcomes, low toxicity when given using partial breast irradiation techniques, and with acceptable cosmetic outcomes.

A number of studies have reported outcomes following rBCS with PBI for the treatment of local breast cancer recurrence; however, this literature is limited to small experiences.^{51–58} Despite this, the data have demonstrated the feasibility of rBCS with re-irradiation as an alternative to SM for selected patients.

Today, PBI has evolved into the armamentarium of the radiation oncologist in the setting of newly diagnosed breast cancer with increasing acceptance in the setting of re-irradiation after repeat lumpectomy. The NRG Oncology RTOG 1014 is a prospective phase 2 trial of three-dimensional conformal external beam (3D-CRT) PBI after rBCS for in-breast recurrence after previous whole breast irradiation.⁵⁹ The primary endpoint of the study was to evaluate skin, breast, and chest wall adverse events occurring within 1 year of completion of re-irradiation therapy. Patients included in the study had unicentric tumors measuring ≤ 3 cm and without evidence of skin involvement as confirmed by magnetic resonance imaging. Documentation of a negative metastatic workup was required, excision margins were negative (no tumor on ink), and patients with 0–3 positive axillary nodes without extracapsular extension were eligible for enrollment. Radiation was targeted to the surgical cavity plus 1.5 cm in a prescription dose of 45 Gy in 1.5 Gy twice daily for 30 treatments. Sixty-five patients were accrued, and the first 55 were included in the analysis. Treatment-related skin changes, fibrosis, and/or breast pain were recorded as grade 1 in 64% and grade 2 in 7%. Only one patient had a grade ≥ 3 adverse event. The study demonstrated acceptable toxicity and safety of a rBCS with re-irradiation using PBI. The secondary endpoints of the study, which include LR, cosmesis, and circulating tumor cells, are awaited.

Techniques, such as limited field radiation, radiation with hyperthermia, and radiation concurrent with chemotherapy, have been described for high-risk patients after SM or excision of chest wall recurrence with promising results thus far.^{60–62}

Adjuvant Systemic Therapy

Until more recently, data regarding the role of chemotherapy following local treatment of breast cancer recurrence has been limited. Early results investigating the use of chemotherapy in chest wall and regional recurrence were disappointing, showing no difference in local control rates in patients receiving systemic therapy.^{63,64} However, results of the CALOR (Chemotherapy as Adjuvant for Locally Recurrent breast cancer) trial demonstrate a survival benefit for a subset of patients with recurrent breast cancer. The trial was an open-label, randomized trial, which included 162 patient with completely excised (mastectomy or lumpectomy with clear margins) isolated

locoregional recurrence after unilateral breast cancer.⁶⁵ Patients were randomized to receive chemotherapy or no chemotherapy stratified by prior chemotherapy, hormone receptor status, and location of recurrence. Chemotherapy regimen was selected by the individual investigator. Patients with estrogen receptor (ER) + and/or progesterone receptor-positive tumors received adjuvant endocrine therapy, radiation therapy was mandated for patients with microscopically involved surgical margins, and anti-HER-2 therapy was optional. The primary endpoint was DFS. Secondary endpoints were OS, sites of first recurrence after randomization, incidence of second (non-breast) malignancies, and causes of deaths without relapse of breast cancer. After a median follow-up of 4.9 years, a significant improvement in DFS and OS were noted in the chemotherapy group compared with the no chemotherapy group (69% vs. 57%, hazard ratio [HR] = 0.59, $p = 0.46$ and 88% vs. 76%, $p = 0.024$ respectively). This benefit was mostly seen in ER – disease (5-year DFS of 67% vs. 35% for ER – disease, HR, 0.32; 95% CI, 0.14–0.73 and 70% vs. 69% for ER + disease HR, 0.94; 95% CI, 0.47–1.89). The results of the final analysis of the trial were published in 2018 confirmed the findings of the earlier analysis.⁶⁶ At a median follow-up of 9 years, chemotherapy improved DFS and OS substantially in ER – (70% vs. 34%) versus ER + (50% vs. 59%) patients. The improvement in DFS by chemotherapy remained significant in the multivariate analysis when adjusting for ER status, location of recurrence, previous chemotherapy use, and interval from primary surgery. The study concluded that chemotherapy benefits patients with resected ER – isolated locoregional recurrences, whereas the addition of chemotherapy to endocrine therapy offers no benefit in patients with ER + disease.

For patients with hormone-positive disease, adjuvant endocrine therapy is recommended. The long-term results of a randomized trial of tamoxifen compared with observation after complete excision of isolated locoregional recurrence and radiation therapy showed that at a median of 11.6 years of tamoxifen improved DFS (6.5 vs. 2.7 years in the observation group, $p = 0.053$, 5-year DFS 61% vs. 40% respectively).⁶⁷ The positive impact of tamoxifen on DFS, however, did not translate into a survival benefit.

CONCLUSIONS

The approach to the management of breast cancer LR is evolving with increased acceptance of rBCS in carefully selected cases: SM with reconstruction, rSLNB, and repeat radiation may be viable options. Patient-related factors, patient expectations, and disease-free interval are

important considerations. A multidisciplinary approach to these cases is key. The management and shared decision process must take into consideration prior local and systemic therapies as well as patient preference.

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