Introduction

Breast cancer is the most common malignancy in women globally (1,2). With the promotion of breast cancer screening, the proportion of breast cancer patients diagnosed at an early stage is increasing. While the effective removal of the tumor was once the primary goal of breast cancer surgery, improving the appearance and function of the breast while maintaining or even improving the same curative effect has become increasingly important in modern surgical treatments. There are two approaches to breast cancer surgery: total mastectomy and breast-conserving surgery. According to the extent of skin resection, total mastectomy can be further divided into traditional total mastectomy, skin-sparing mastectomy (SSM), and nipple-areola-complex-sparing mastectomy (NSM).

The removal of the nipple-areola complex (NAC) can result in physical and psychological distress for patients (3). Although the appearance of the breast can be further improved by secondary NAC reconstruction...
with oncoplastic breast surgery (OBS) (4), patients with reconstructed nipples generally experience low satisfaction and poor psychosocial and sexual well-being (5). Compared with post-mastectomy breast reconstruction, NSM can not only preserve the integrity of the NAC and optimize cosmetic outcomes, but it is also an oncologically safe surgical procedure that can reduce patient morbidity (6,7). However, surgeons have yet to reach a consensus regarding some key aspects of the safety of NSM, including whether the rate of local recurrence is acceptable with NSM and whether it should be performed alone or in combination with local radiotherapy (RT).

Pre-, intra-, and/or postoperative RT is commonly performed for the management of breast cancer. Adjuvant RT following breast-conserving surgery helps to reduce the risk of local recurrence in the residual glands. However, the role of adjuvant RT after NSM remains unclear.

In this article, we review the application of RT in NSM and compare studies on NSM combined with pre-, intra- and/or postoperative RT. Additionally, we analyze the criteria for selecting suitable patients for NSM and discuss some controversial key issues on the future application of radiotherapy in NSM. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/abs-20-77).

Search strategy

A literature search was conducted on PubMed using a combination of the keywords: “reconstruction”, “breast cancer”, “nipple-areola complex-sparing mastectomy”, “preoperative radiotherapy”, “intraoperative radiotherapy”, and “postoperative radiotherapy”.

All types of articles were included. Non-English language articles for which only an abstract was available were excluded. The search was carried out in June, 2020; due to the limited amount of existing research on this topic, no date restrictions were applied.

The status of radiotherapy in NSM

Nielsen et al. were the first to suggest the idea of using RT with NSM (8). They reported that RT could reduce the risk of recurrence of breast carcinoma after breast-conserving surgery. The NAC is the gathering area of the breast ducts, and the subcutaneous tissue in this area is an important transit station in the process of breast lymphatic reflux. Therefore, NAC and subcutaneous tissue in this area can be overlooked as sites for cancer cells. Moreover, the small amount of breast ductal tissue remaining at the base of the NAC after NSM is considered to be a risk factor for postoperative local recurrence. Therefore, adjuvant radiotherapy is recommended to reduce the local rate of recurrence after NSM, especially for patients with a high risk of local recurrence in the NAC (9,10).

Conventional postoperative radiotherapy (PORT) for breast cancer can lead to contraction deformation of the implanted prosthesis. Radiotherapy-assisted NSM combined with breast reconstruction has been optimized by the emergence of intraoperative radiotherapy (IORT) technology, which can effectively kill the residual tumor cells by delivering a single high dose of radiation to the target during the operation. Compared with PORT, the advantage of IORT is that it has more precise delivery and, thus, reduces the damage to surrounding tissues (11-14). Because the skin and subcutaneous tissue are not irradiated during IORT treatment, the risk of fibrosis is lower, which entails better cosmetic postoperative outcomes (15-19).

Trials of preoperative RT combined with NSM

Many studies have focused on patients who underwent RT following breast reconstruction surgery. Alperovich et al. (20) focused specifically on patients who underwent NSM with neoadjuvant RT. Theirs was the largest study to evaluate reconstruction using NSM with pre-operative radiotherapy. Of 501 breasts, 26 were irradiated. No statistically significant differences were observed in flap necrosis, NAC, implant explantation, hematoma formation, or capsular contraction between breasts that received and did not receive RT.

Reish et al. (21) compared the outcomes of 605 patients who underwent NSM. Of them, 88 patients received RT; 43 and 45 patients were treated with preoperative and postoperative RT, respectively. The 2-year follow-up results showed that preoperative RT had a higher risk of total complications [P=0.04; odds ratio (OR), 2.225; 95% confidence interval (CI), 1.040–4.758], while postoperative RT had a higher risk of explantation (P=0.015; OR, 5.634; 95% CI, 1.405–22.603). Patients who received RT were more likely to require secondary procedures for capsular contracture or fat grafting. The total nipple retention rate in patients treated with RT was 90%, and the reconstruction failure rate was 8%.

However, a 2014 study by Colwell et al. (22) produced conflicting results. The study included 285 patients who
underwent NSM, including 77 patients who received preoperative RT. The results of this study suggested that preoperative RT is associated with NAC necrosis (OR, 4.86; 95% CI, 1.0197–23.169).

**Trials of IORT combined with NSM**

Traditional whole-breast external beam radiation therapy (EBRT) is typically delivered for 5–7 weeks after surgery. EBRT can lead to pigmentation and atrophy of the skin, which affect the appearance of the breast, as well as damage to organs adjacent to the irradiation site (23). IORT is a form of accelerated partial breast irradiation (APBI) that can deliver a single high dose of radiation directly to the visibly identifiable tumor bed, while limiting radiation exposure for the rest of the breast (24). Due to its high target dose and uniform dose distribution, IORT can improve the radiobiological effect, meaning it may reduce the rate of local recurrence with NSM. IORT has been used in the treatment of patients undergoing breast-conserving surgery and NSM surgery. IORT has the advantages of precise radiotherapy delivery, good protection of healthy tissues and organs, and acceptable cosmetic effects. Therefore, IORT is regarded as an alternative to EBRT as an adjuvant treatment with breast-conserving surgery.

Two famous international clinical studies have been carried out on breast-conserving surgery to date: the TARGeted Intraoperative radiotherapy-Alone (TARGIT-A) trial (25) and the intraoperative electron radiation therapy (ELIOT) trial (26). Inspired by these two clinical trials, intraoperative electron radiation-NSM (ELIOT-NSM) and TARGeted Intraoperative radiotherapy-NSM (TARGIT-NSM) were launched to explore the feasibility of IORT-NSM.

**ELIOT-NSM**

The European Institute of Oncology (IEO) in Italy reported that the combination of NSM with the delivery of IORT to the NAC may reduce the risk of local recurrence (27). The ELIOT with NSM trial was initiated by the IEO in 2002. It is the first study to report the feasibility of NSM combined with breast reconstruction assisted by single radiotherapy. The inclusion criteria were: primary tumors located within 1 cm of the areola margins; the absence of nipple retraction; the absence of bloody discharge; and the absence of retroareolar microcalcifications.

During the operation, the tissue behind the NAC was obtained for frozen pathological examination. If the frozen pathology result was positive, then the NAC was removed; if the result was negative, ELIOT was delivered to the NAC and the areas 1 cm outside the areola margins. Results published in 2009 involved 1,001 patients including 800 who received ELIOT and 201 who underwent delayed one-shot RT on the day following the operation. The median follow-up was 20 months, and the local recurrence rate was only 1.4%. Of the 14 cases of local recurrence, 10 cases were located near the primary tumor site and no cases were near the NAC. The patients rated the cosmetic appearance on a scale ranging from 0 (bad) to 10 (excellent), and the median score was 8. The incidence of infection and necrosis in the study was 2–10% (28).

In 2012, IEO updated the results of ELIOT-NSM with a median follow-up of 50 months. Of the 934 patients included in the study, 861 received radiotherapy, and only 1.3% experienced recurrence at the NAC site (29). In 772 patients with invasive carcinoma, the rate of local recurrence in the breast and the NAC was 3.6% and 0.8%, respectively. In the 162 patients with intraepithelial neoplasia, the rate of local recurrence in the breast and the NAC was 4.9% and 2.9%, respectively.

**TARGIT-NSM**

Pan et al. (30) first introduced Intrabeam® IORT in NSM with breast reconstruction in 2014. In their latest study, published in 2019 (7), 41 patients who underwent NSM surgery with Intrabeam® IORT (16 Gy) followed by breast reconstruction were enrolled. After a median follow-up of 26 months, no IORT-induced lung or cardio injury, local recurrence, or metastasis was observed.

**Trials of PORT combined with NSM**

PORT delivered to reconstructed breasts has been repeatedly evidenced to heighten the risk of complications, including radiation fibrosis and prolonged pigmentation, as well as poor cosmetic results (31,32). The application of PORT after NSM surgery is not common, and the number of patients who receive NSM combined with PORT reported in the literature is small. A consensus has not been reached on the impact of PORT on NSM (32).

Benediktsson et al. (33) carried out a prospective, controlled study in 2007, enrolling 216 patients treated with NSM. After a median follow-up of 13 years, the 10-year overall survival rate was 80.5%. Of the patients in the study, 47 received adjuvant RT. The local recurrence rate...
in patients who received RT was 8.5%, compared to 28.4% among patients who did not receive RT. The results showed that RT could reduce the local recurrence rate.

In a report published in 2015, Tang et al. analyzed treatment outcomes in a large cohort of 982 patients who underwent NSM plus immediate reconstruction. Of the patients, 67 received preoperative RT and 97 received PORT. Patients who underwent preoperative RT and those who underwent PORT experienced more overall complications (10.2% vs. 21.7% and 17.5%, P=0.003, 0.03, respectively) and nipple loss (0.9% vs. 4.3% and 4.1%, P=0.04, 0.02, respectively) than patients not treated with RT, while PORT was also associated with a higher rate of reconstruction failure (2.2% vs. 8.2%, P=0.003) (34).

However, some studies have arrived at the opposite conclusion. A literature review by Janssen et al. (35) found that only 7 studies of NSM provided detailed RT information, and none of these studies reported increases in the rates of partial or complete NAC necrosis following adjuvant RT. Zheng et al. (36) reported the same result in their meta-analysis, indicating that RT had no effect on NAC.

**Patient selection criteria in different studies**

Table 1 summarizes the studies of different NSM, with pre-, intra- and/or postoperative RT. In most studies, the size of the tumor was <3 cm, and the distance between the tumor and the nipple was at least 1 cm. Patients with a low risk of recurrence might not need RT. Protective factors for recurrence include: the tumor treated with NSM being small and far enough from the NAC; no tumor involvement observed in the tissue below the frozen nipple during the

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Radiotherapy/n</th>
<th>Method</th>
<th>NAC necrosis/%</th>
<th>LR/%</th>
<th>Selection of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alerovich, 2014</td>
<td>501</td>
<td>26</td>
<td>Pre-operative</td>
<td>Complete</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Colwell, 2014</td>
<td>285</td>
<td>77</td>
<td>Pre-operative</td>
<td>4.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Petit, 2012</td>
<td>934</td>
<td>900</td>
<td>ELIOT (n=875)</td>
<td>–</td>
<td>–</td>
<td>Invasive carcinoma: 3.6% breast vs. 0.8% NAC; intraepithelial neoplasia: 4.9% breast vs. 2.9% NAC</td>
</tr>
<tr>
<td>Petit, 2009</td>
<td>1,001</td>
<td>1,001</td>
<td>ELIOT (n=800)</td>
<td>NAC total</td>
<td>1.4</td>
<td>No recurrence was observed in the NAC</td>
</tr>
<tr>
<td>Poruk, 2015</td>
<td>130</td>
<td>36</td>
<td>EBRT</td>
<td>–</td>
<td>0.8</td>
<td>Primary tumor located at least 2 cm away from the NAC skin</td>
</tr>
<tr>
<td>Benediktsson</td>
<td>216</td>
<td>47</td>
<td>EBRT</td>
<td>0.1</td>
<td>8.5</td>
<td>A tumor size &gt;3 cm</td>
</tr>
<tr>
<td>Gerber, 2009</td>
<td>60</td>
<td>16</td>
<td>EBRT</td>
<td>–</td>
<td>11.7</td>
<td>no skin involvement, and tumor margins &gt;2 cm from the nipple</td>
</tr>
</tbody>
</table>

**NSM, nipple-areola-complex-sparing mastectomy; LR, local recurrence; NAC, nipple-areola complex-sparing; EBRT, external beam radiation therapy.**
operation; and the sentinel lymph nodes observed to be negative during the operation. If the patients with high risk of recurrence undergo NSM, then the NAC and regional lymph nodes should be followed up with adjuvant RT. Risk factors for recurrence include: ≥4 positive axillary lymph nodes and a tumor size >5 cm. For patients with moderate risk of recurrence (1–3 metastatic lymph nodes), the effect of radiotherapy on cosmetic results should be considered before NSM is chosen.

**Complications**

Complications of conservative mastectomies with immediate reconstruction are the same as those of non-conservative mastectomies and include wound dehiscence, infection, implant loss, asymmetry, and capsular contracture. The main complications are fat necrosis, radiation fibrosis, prosthesis contracture and pain (37,38). For patients receiving radiation treatment after autogenous reconstruction, the complication rate ranges from 5–16%, with fat necrosis (16%) and fibrosis (11%) being the complications encountered most frequently (39). Patients with breast implants who receive RT are likely to develop capsular contracture, with capsulotomy required in up to 43% of patients (40). Thus, some surgeons choose to expand the volume of the breast reconstruction slightly when performing breast reconstruction for patients who require RT after surgery.

According to the IEO study published in 2012, 48 patients did not undergo intra-or postoperative RT, mainly because of the poor blood supply to the NAC after subcutaneous mastectomy. The IEO Center analyzed the necrosis rate of NAC in 1001 other patients who received NSM and intraoperative radiotherapy; the total necrosis rate of NAC was 3.5%, the partial necrosis rate was 5.5%, and the remaining NAC was removed in 50 cases (35) due to various complications (28).

**Conclusions and perspectives**

NSM has become significantly more common in recent years. There is abundant evidence in the literature that NSM can obtain a better appearance of the breast and improve quality-of-life for patients. Meanwhile, NSM reduces the need for additional nipple reconstruction and provides an acceptable level of oncologic safety. Based on the treatment principle of NSM, the selection of patients and the quality control of the operation underpin the entire treatment. The application of pre-, intra-, and/or postoperative RT and its specific impact on the NAC is still a grey zone in the literature. Considering the limited number of cases and the short follow-up times of the studies reported here, more randomized controlled studies with a larger sample size and longer follow-up are needed to evaluate the long-term efficacy of NSM with RT. More clinical studies and data are needed to explore the feasibility of combined RT, and the type and dose of RT required.

**Ackowledgments**

**Funding:** None.

**Footnote**

Provenance and Peer Review: This article was commissioned by the Guest Editor (Edward I. Chang) for the series “Novel Innovations and Advancements in Breast Reconstruction” published in *Annals of Breast Surgery*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the NARRATIVE REVIEW reporting checklist. Available at http://dx.doi.org/10.21037/abs-20-77

Peer Review File: Available at http://dx.doi.org/10.21037/abs-20-77

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/abs-20-77). The series “Novel Innovations and Advancements in Breast Reconstruction” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the
original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References


(English Language Editor: J. Reynolds)