Review Article

Narrative review of the application of radiotherapy in nipple-areola-complex–sparing mastectomy

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Abstract: In the treatment of breast cancer, the effective removal of the tumor was once the sole aim of surgery. However, the goals of breast cancer surgery have shifted, with considerable emphasis now placed on improving the appearance and function of the breast while leaving the curative effect unaffected or even improved. Nipple-areola-complex-sparing mastectomy (NSM) facilitates breast reconstruction by preserving the skin and nipple-areola complex (NAC) of the breast. In recent years, this approach has become increasingly popular; however, it still carries a high risk of local recurrence in the NAC. Therefore, for patients who NSM, adjuvant radiotherapy (RT) is recommended. Although adjuvant radiation therapy is the standard of care for breast cancer treatment following lumpectomy, the application of RT after NSM is controversial. Previous studies on the roles of pre-, intra-, and/or postoperative RT combined with NSM have produced inconsistent results. Conventional preoperative or postoperative RT for breast cancer can cause contracture deformation of the implanted prosthesis. The emergence of intraoperative RT technology has further optimized radiotherapy-assisted NSM combined with breast reconstruction as a therapeutic strategy for breast cancer. The main complications of this treatment include fat necrosis, radiation fibrosis, and prosthesis contracture. Based on the selection of suitable patients, adjuvant RT is applied in combination with NSM according to the risk of local disease recurrence. In this article, we review the application of RT in NSM and compare studies on NSM combined with pre-, intra-, and/or postoperative RT.

Keywords: Early-stage breast cancer; nipple-areola-complex-sparing mastectomy (NSM); radiotherapy (RT)

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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 contracture 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 retro areolar 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

Table 1 The treatments and rates of local recurrence in different studies on NSM

Author	N	Radiotherapy/n	Method	NAC necrosis/%	LR/%	Selection of patients
Alperovich, 2014 (20)	501	26	Pre-operative	Complete necrosis: 3.8; partial necrosis: 3.8	–	–
Colwell, 2014 (22)	285	77	Pre-operative	4.4	–	–
Petit, 2012 (29)	934	900	ELIOT (n=875) *vs.* EBRT +/-ELIOT (n=25)	–	Invasive carcinoma: 3.6% breast *vs.* 0.8% NAC; intraepithelial neoplasia: 4.9% breast *vs.* 2.9% NAC	Tumor located outside the areola area, no nipple retraction, no blood discharge from the nipple, no inflammatory signs, no previous irradiation, no microcalcifications, and frozen retro areolar section negative for carcinoma
Petit, 2009 (28)	1,001	1,001	ELIOT (n=800) *vs.* delayed ELIOT (n=201)	NAC total necrosis: 3.5%; NAC partial necrosis: 5.5%.	1.4 No recurrence was observed in the NAC	Ibid
Pan, 2014 (30)	41	41	TARGIT	0	0	Primary tumor or microcalcifications located in the central portion of the breast, at least 1 cm away from the NAC skin
Poruk, 2015 (37)	130	36	EBRT	–	0.8	Primary tumor located at least 2 cm away from the NAC skin
Benediktsson 2008 (33)	216	47	EBRT	0.1	8.5	A tumor size of >3 cm
Gerber, 2009 (38)	60	16	EBRT	–	11.7	no skin involvement, and tumor margins >2 cm from the nipple

NSM, nipple-areola-complex-sparing mastectomy; LR, local recurrence; NAC, nipple-areola complex-sparing; EBRT, external beam radiation therapy.

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

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.

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