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ORIGINAL ARTICLE

Oncologic outcomes and radiation safety of nipple-sparing mastectomy with intraoperative radiotherapy for breast cancer

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Abstract

Background Nipple-sparing mastectomy combined with breast reconstruction helps to optimize the contour of the breast after mastectomy. However, the indications for nipple-sparing mastectomy are still controversial. Local radiation to the nipple–areola complex may play some roles in improving the oncological safety of this procedure.

Methods From January 2014 to December 2017, 41 consecutive patients who underwent nipple-sparing mastectomy combined with Intrabeam intraoperative radiotherapy to the nipple–areola complex flap and breast reconstruction were enrolled in this prospective study. The prescribed radiation dose at the surface of the spherical applicator was 16 Gy.

Results In eight cases, carcinomas were in the central portion of the breast. Partial necrosis of the nipple–areola complex occurred in three cases. Over 90% of patients reported "no or poor sensation" of the nipple–areola complex postoperatively. With a median follow-up time of 26 months, no recurrences or metastases were identified; however, breast-cancer mortality occurred in one patient. Pathologic evaluation of paraffin-embedded sections showed ductal carcinoma in situ in the remaining tissues deep to the nipple–areola complex flap in two patients. Although no further treatment was administered to the nipple–areola complexes postoperatively, no recurrences or metastases were identified 20 months and 24 months later, respectively. Optical microscopy and transmission electron microscopy revealed changes in some normal tissues immediately after Intrabeam intraoperative radiotherapy. Karyopyknosis were observed in gland tissues, and the collagenous fibers became sparse and arranged chaotically. As assessed by thermoluminescence, radiation doses at different sites in the nipple–areola complex flap varied considerably and were about 10 Gy at the areola surface. No Intrabeam intraoperative radiotherapy-related acute or chronic radiation injuries of the lung, heart or bone marrow were identified.

Conclusions Our findings indicate that Intrabeam intraoperative radiotherapy during nipple-sparing mastectomy combined with breast reconstruction is safe and feasible.

Trial registration The current study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (registering order 201750). All participants gave their written informed consent.

Keywords Breast cancer · Intraoperative radiotherapy · Nipple-sparing mastectomy · Radiation injury · Dose distribution

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Abbreviations

NSM	Nipple-sparing mastectomy
NAC	Nipple–areola complex
IORT	Intraoperative radiotherapy
EBRT	External beam radiotherapy
RTOG	Radiation Therapy Oncology Group
HE	Hematoxylin and eosin
TEM	Transmission electron microscope
DCIS	Ductal carcinoma in situ

Introduction

Since the initial radical mastectomy, surgery for breast cancer has been developing continuously. The topic that is currently receiving increasing attention is how to best preserve the contour and function of breast without compromising the efficacy of standard treatments, or even improving it [1]. Nipple-sparing mastectomy (NSM) has been a research hotspot in many Breast Surgery Departments in the past 10 years [2–14].

Currently, the safety of NSM is still controversial and inclusion criteria vary between institutions. The probability of cancer cell infiltration in the nipple–areola complexes (NAC) of mastectomy specimens is reportedly between 0 and 58% (under 20% in most studies) [15–21]. The local recurrence rate in patients with primary breast cancer who have undergone NSM is reportedly between 0 and 28.4% (< 5% in most studies) [2–11, 22–26]. Moreover, the false negative rate of intraoperative frozen section analysis of NAC basal tissue is between 1.5 and 9.3% [6, 27, 28]. Because of limitations in sampling, failure to identify cancer cells in the NAC basal tissues of operative specimens does not exclude the possibility of residual cancer cells in NAC flaps.

As one of the adjuvant therapies associated with breast-conserving surgery, radiotherapy is helpful in reducing the local recurrence rate, including in the NAC, and improving survival [29]. Limited studies have investigated the influences of intraoperative radiotherapy (IORT) or external beam radiotherapy (EBRT) on NSM. Benediktsson et al. [6] found that the local recurrence rates of patients given EBRT after NSM associated with breast reconstruction was significantly lower than those of patients who did not receive EBRT (8.5% vs. 28.4%, $P = 0.025$). The ELIOT clinical trial [30] reported a local recurrence rate at a median of 20 months' follow-up in patients who had undergone NSM combined with IORT of only 1.7% (14/830) and there were no NAC recurrences. In our preliminary study [31], Intrabeam® IORT was employed during NSM combined with breast reconstruction. The median duration of follow-up was 7 months and no recurrences were identified.

IORT is characterized by a small effective irradiation target volume and high single-dose of radiation, which has little effect on the tissues outside the irradiation target. Computer-simulated irradiation dose attenuation curve of IORT shows that the radiation dose to the deep viscera from IORT-associated NSM is very low [31]. To the best of our knowledge, there are no detailed reports on the radiation doses at different sites during IORT or objective data on acute (< 3 months) and chronic (> 1 year) radiation injuries caused by IORT.

On the basis of findings of our previous study [31], we expanded the surgical indications. We preliminarily explored oncologic safety by analyzing medium-term follow-up data on patients treated with Intrabeam IORT associated with NSM combined with breast reconstruction. We also studied the influences of Intrabeam IORT on the morphology of normal tissues deep to the NAC flap and radiation safety.

Materials and methods

The current study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (registering order 201750). All participants gave their written informed consent. IORT was administered using an Intrabeam® device (PRS 500; Carl Zeiss, Oberkochen, Germany).

Patient selection

From January 2014 to December 2017, consecutive women with breast cancer undergoing NSM combined with IORT and breast reconstruction were enrolled in this study. All participants were admitted to the Breast Surgery Department of the First Affiliated Hospital of Guangzhou Medical University. Inclusion and exclusion criteria have previously been described [31]. Additional inclusion criteria also included bilateral breast carcinoma; primary tumor or suspicious microcalcifications located in the central portion of the breast, but at least 2 cm away from the NAC skin according to mammography or MRI in a prone position, and/or at least 1 cm away from it according to sonography; intraoperative retro-areolar frozen section analysis was not necessary; clinical stages T0–2, N0–1, and M0. In patients with N0 by clinical staging who were to receive neo-adjuvant chemotherapy, it was suggested that an axillary sentinel lymph node biopsy be taken before starting chemotherapy.

Surgical and IORT procedures

The surgical and IORT procedures were almost the same as previously described [31]. NSM was undertaken first, starting with a short arc peri-areolar (Fig. 1a) or radial incision

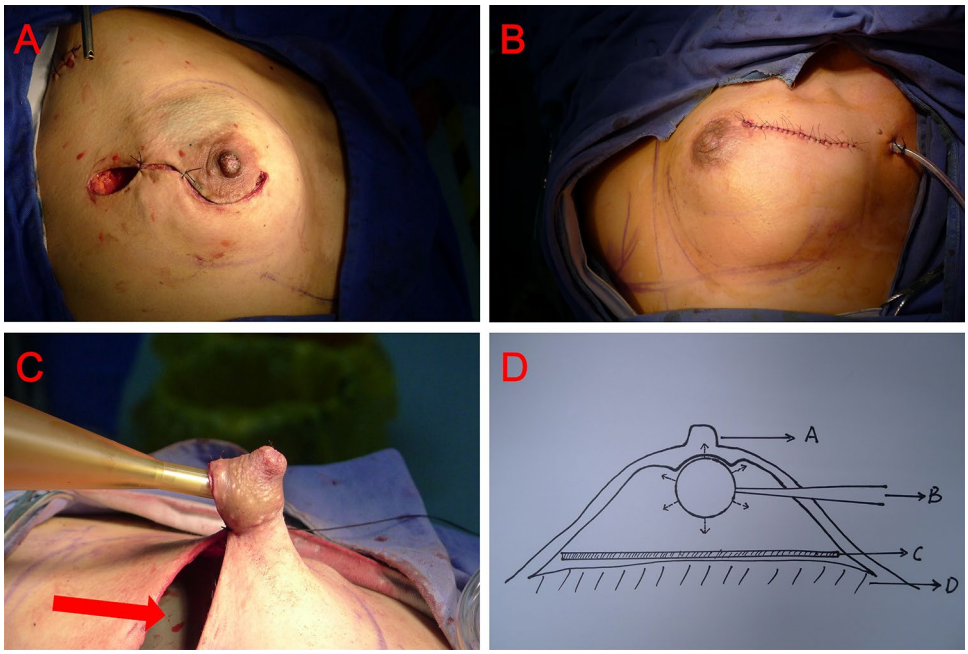

Fig. 1 Intraoperative photographs and a diagram showing the incisions and intraoperative radiotherapy

(Fig. 1b). The preserved areola flap was usually 4–5 mm thick. For Asian women, a spherical applicator of diameter 2.5 or 3.0 cm was usually chosen. To achieve a uniform radiation dose, the edge of NAC flap was sutured to hold the pliable flap to the applicator surface (Fig. 1c). As shown in Fig. 1c, d, a piece of shielding material (tungsten-filled polyurethane) could be placed on the pectoralis major; this was optional. A single radiation dose of 16 Gy at the surface of the spherical applicator was then administered. After IORT, breast reconstruction with a silicone gel-filled breast implant was performed on women for whom postoperative radiotherapy was not planned. Otherwise, breast reconstruction with an expander was undertaken. For the patients that undertook an expander implantation and needed external beam radiotherapy postoperatively, three-dimensional conformal radiotherapies were applied, limiting the amount of radiation absorbed in the NAC flap as much as possible.

Outcomes

Outpatient follow-up was scheduled every 3–6 months for the first 5 years. The primary endpoints were relapse-free survival and necrosis of the NAC. The secondary endpoints included metastasis-free survival, overall survival, acute/chronic radiation injury, degree of sensation in the NAC, wound complications, and breast contour. As previously described [31], scores of NAC sensation were divided into no sensation, poor, medium, and good; scores of breast contour were divided into poor, medium, and good.

IORT-induced radiation injury to the lung, heart, and bone marrow

Data for evaluating acute (< 3 months) and chronic (> 12 months) radiation injury to the lung, heart, and bone marrow included lung- and heart-related symptoms, left ventricular ejection fraction, electrocardiogram, chest X-ray film, troponin I concentration, white blood cell, neutrophil, and platelet counts, and hemoglobin concentration (only for chronic radiation injury). Data were obtained before surgery (baseline), ≤ 3 months after surgery (or before commencement of adjuvant chemotherapy/EBRT), and ≥ 12 months after surgery (if no chemotherapy/EBRT had been administered). Radiation injury was diagnosed in the presence of any of the following: Left ventricular ejection fraction decreased by more than 20%. Troponin I concentration became abnormal (> 0.04 μg/L). In accordance with the criteria for radiation injury of the Radiation Therapy Oncology Group (RTOG) [32], grades for heart, lung, or blood cells changed by ≥ 1 level.

Morphological changes in normal tissues after IORT

In selected patients, 2 × 2 × 1 mm and < 2 × 1 × 1 mm samples of tissues deep to the NAC flap were sharply dissected (to minimize impact on blood supply) for hematoxylin and eosin (HE) staining and transmission electron microscope (TEM) assessment, respectively. At least two specimens (≤ 5 min before and after IORT) were obtained from the same area of the NAC flap in each case, that is, the area that was directly irradiated. In some cases more specimens were obtained after removal of the mammary tissues while

waiting for IORT to be administered. Such specimens were obtained from 16 and 5 patients for HE staining and TEM observation, respectively.

For HE staining, specimens were fixed in 10% buffered neutral formalin. Paraffin-embedded sections, 4 μm in thickness, were examined after HE staining by two pathologists.

For TEM imaging, specimens were fixed in 2.5% glutaraldehyde/0.1 M phosphate buffer (precooled at 4 °C) for more than 2 h and post-fixed in 1% osmium acid/0.1 M phosphate buffer (precooled at 4 °C) for 2 h. Following gradient dehydration and embedding, ultrathin sections (60 nm) were then cut using a microtome. Sections were stained with uranyl acetate and lead citrate and then examined under an electron microscope (JEM-1400 PLUS, Tokyo, Japan).

Measuring radiation dose distribution

High sensitivity LiF (Mg, Cu, P) thermoluminescence chips (Guangdong Province Institute of Radiation Injury, Guangzhou, China) were used to measure radiation dose distributions. The thermoluminescence material was powdery and, therefore, enveloped in small transparent plastic packages (Fig. 2a, b). After irradiation, the dose absorbed by the chips was measured using a FJ427A1 type microcomputer thermoluminescence dosimeter (Beijing Nuclear Instrument, Beijing, China).

In preparation for administering IORT, the chips were numbered and soaked in 70% alcohol for 5 min, after which they were wrapped in a piece of sterile membrane. A piece of very thin shielding material (tungsten-filled polyurethane, 0.7 mm in thickness) was then placed on the pectoralis major. The chips were then placed at the following six sites simultaneously (Fig. 2a, b): the tip of nipple; the areolar surface; the skin surface 2 cm away from the areolar margin; the surface of the shielding material; the space between shielding material and pectoralis major; and surface of the spherical applicator facing the non-irradiated region. The prescribed radiation dose at the surface of the spherical applicator was 16 Gy and the radiation was expected to attenuate sharply in a spherical manner (Fig. 2a).

To avoid exceeding the linear measurement range of the thermoluminescence materials, they were replaced four times during IORT; thus, the radiation dose was the sum measured by all chips placed at each site. Because the accuracy with which thermoluminescence materials measure radiation dose is inferior to that measured by an ionization chamber (a calibration device for Intrabeam), the actual radiation dose (D_a) at each site was corrected by adjusting with the measurements obtained at each (D_m) and at the surface of the spherical applicator (D_0). D_a (Gy) $= 16 \times D_m/D_0$. Additionally, to determine the background signal unrelated to the irradiation, another chip was placed outside the operation room during IORT.

Results

General informations

Three of the forty-four women enrolled initially were excluded during surgery because of the positive results by frozen section analysis; thus, 41 patients were assessed. All 41 patients had unilateral breast cancer and were of median age 41 years (quartile range 35–45 years). Thirty-seven patients underwent unilateral NSM combined with breast reconstruction, and 32 of them also underwent immediate breast reconstruction. The remaining four patients additionally underwent prophylactic contralateral NSM (without

Table 1 Description of pathologic TNM staging ($n = 41$)

Stage	Pathologic TNM staging	No. of patients	Median tumor size in greatest dimension (range, mm)
0	TisN0M0	7	36 (26 to > 50)
I	T1N0M0	5	18 (14 to 20)
II	T1N1M0	2	15 and 18
	T2N0M0	14	27 (21 to 36)
	T2N1M0	9	30 (22 to 41)
III	T2N2M0	4	34 (26 to 46)

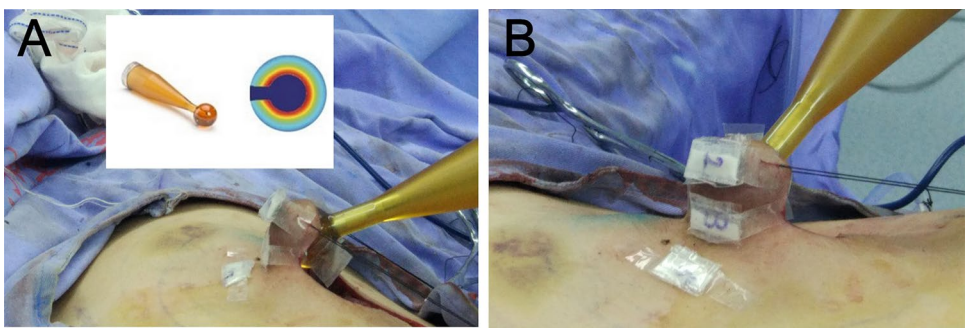

Fig. 2 Radiation dose distributions measured by thermoluminescence chips

IORT) combined with breast reconstruction. Seven of the 41 patients had Stage 0 disease, five Stage I, 25 Stage II, four Stage III, and none Stage IV (Table 1). Invasive ductal carcinoma was diagnosed in most cases (27, 65.9%). In eight cases (19.5%), carcinomas were in the central portion of the breast. Moreover, ten patients (24.4%) received neither chemotherapy nor postoperative radiotherapy.

A 2.5-cm or 3.0-cm spherical applicator was used to administer IORT in 82.9% of the patients, and the median irradiation time was 13 min 35 s. No patient required excision of the NAC because of poor blood supply to the NAC flap during operations.

Follow-up and outcomes

All 41 patients attended regularly for outpatient follow-up (median duration, 26 months; quartile range 15–38 months).

Thirty-four (82.9%) patients had evidence of varying degrees of blood stasis in the NAC flap 1 week after surgery. This resolved spontaneously in most cases; however, the local traction sign remained evident in the NAC skin of some patients. Another three patients (7.3%) had partial necrosis of the NAC. No patient required further surgery to excise the NAC. By the end of follow-up, nine patients (22.0%) were scored as having no sensation in the NAC, 29 (70.7%) as poor sensation, and three (7.3%) as medium sensation. Representative examples of post-operative breast (including NAC) contours are shown in Fig. 3. Cosmetic outcomes were considered medium in 15 patients (36.6%) and good in 26 (63.4%).

By the last follow-up, breast-cancer mortality occurred in one patient (28 months after surgery). The remaining patients had no evidence of local regional recurrence or distant metastasis. The patient who died of lethal metastases was 33 years old when she was first diagnosed with triple-negative breast cancer, pathological stage IIB. Physical examination, color Doppler ultrasound and CT scan 3 months before death revealed no abnormality in the affected breast (including NAC) or chest wall.

Histopathological findings in NAC basal tissues

Intraoperative frozen sections of NAC basal tissue specimens were obtained and examined prior to administration of IORT in 35 of the 41 patients. One (2.9%) was false negative and was subsequently diagnosed as ductal carcinoma in situ (DCIS) by examination of paraffin-fixed sections. For this case, the tumor in the breast was invasive ductal carcinoma. In the remaining six patients, NAC basal tissue specimens were only examined by paraffin-fixed sections. And only one showed a positive result of DCIS, which was the same as the tumor in the breast. The above two patients received NAC IORT and standard systematic treatments after surgery. They retained their NACs and were followed up for 20 months and 24 months, respectively. No recurrence or metastasis was detected.

IORT-induced radiation injury to the lung, heart, and bone marrow

According to baseline and < 3 months follow-up indices of the 41 patients, and ≥ 12 months follow-up indices of eight patients (who received neither chemotherapy nor postoperative radiotherapy), there was no evidence of IORT-induced acute or chronic radiation injury to the lung, heart, or bone marrow.

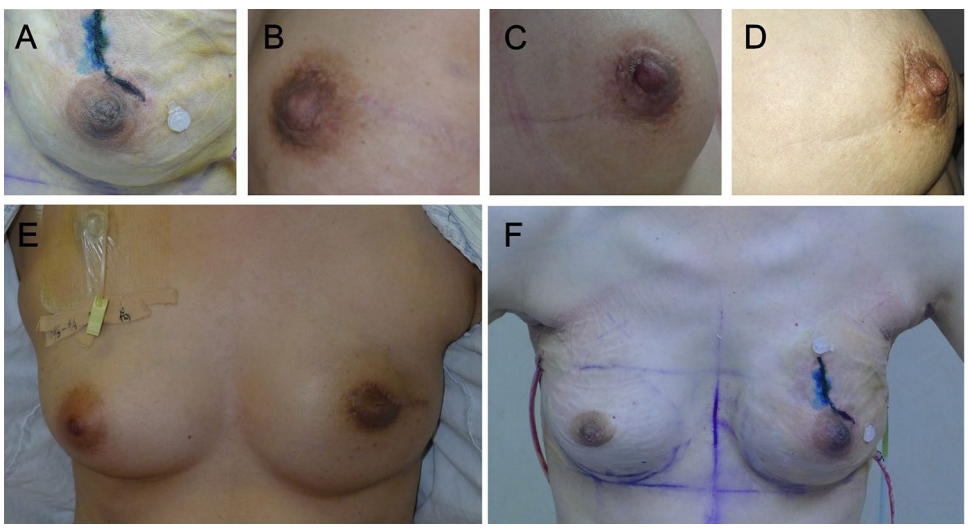

Fig. 3 The contours of breasts after Intrabeam intraoperative radiotherapy during nipple-sparing mastectomy with breast reconstruction. A week after surgery (**a**), 6 months or more after surgery (**b**–**d**), unilateral immediate breast reconstruction (**e**), bilateral immediate breast reconstructions after prophylactic nipple-sparing mastectomy of the right breast (**f**)

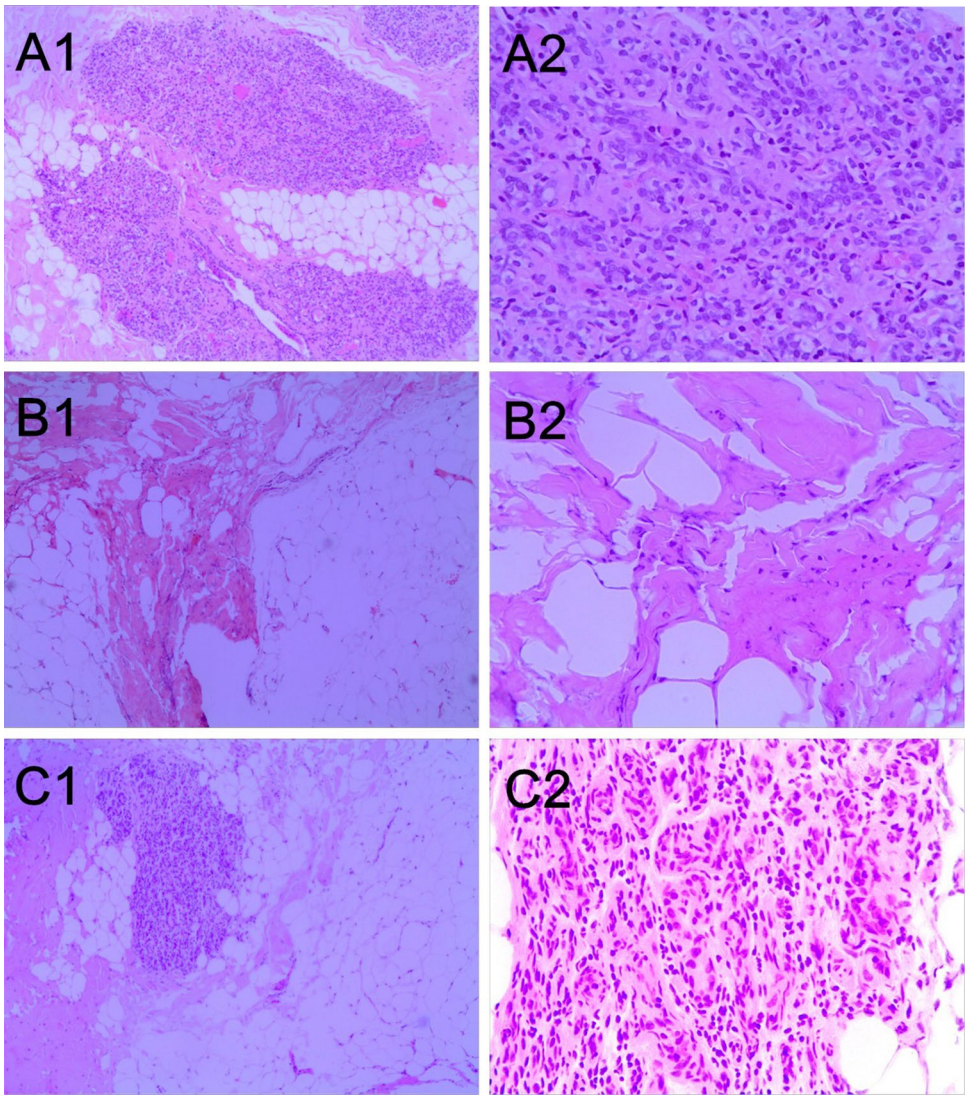

Fig. 4 Photomicrographs showing morphological changes of basal tissues in the nipple areola flap before and after Intrabeam intraoperative radiotherapy. Original magnification, ×50 (**a1–c1**); original magnification, ×200 (**a2–c2**). 30 min after removal of the mammary tissues (**a1, a2**), 60 min after removal of the mammary tissues (5 min before intraoperative radiotherapy) (**b1, b2**), 5 min after intraoperative radiotherapy (**c1, c2**)

Influence of IORT on the morphology of normal NAC basal tissues

Microscopic and TEM examinations revealed that changes of blood supply in the NAC flap within 1 h or a little bit more since the mammary tissues were removed had limited influences on the morphology of normal basal tissues in the NAC flap (Figs. 4a, b, 5a, b). After Intrabeam single large-dose irradiation (16 Gy), some normal basal tissues in the NAC flap showed morphological changes. HE-stained sections showed karyopyknosis of gland tissues, collapse of capillaries, slight swelling of collagenous fibers, and weak staining (Fig. 4c). On TEM examination, the collagenous fibers were found to be sparse and arranged chaotically; the chromatin in the fibroblasts had agglutinated, the nucleolus structure was indistinct, the cell nuclei tended to be pyknotic, and there was little cytoplasm (Fig. 5c).

Radiation dose distributions

Radiation dose distributions in five patients are shown in Table 2. Because the thickness of NAC flap and the length of nipple differed between these patients, there was a wide range of findings. When the irradiation dose on the surface of the spherical applicator was 16 Gy, the irradiation dose through the NAC flap to the areola surface attenuated by 3/10–3/7 and by 4/5–7/8 through the NAC flap to the tip of nipple. The radiation dose at the skin surface 2 cm away from the areola margin was less than 2 Gy. A piece of shielding material (tungsten-filled polyurethane) reduced the radiation dose at the surface of pectoralis major from about 4 Gy to less than 0.1 Gy.

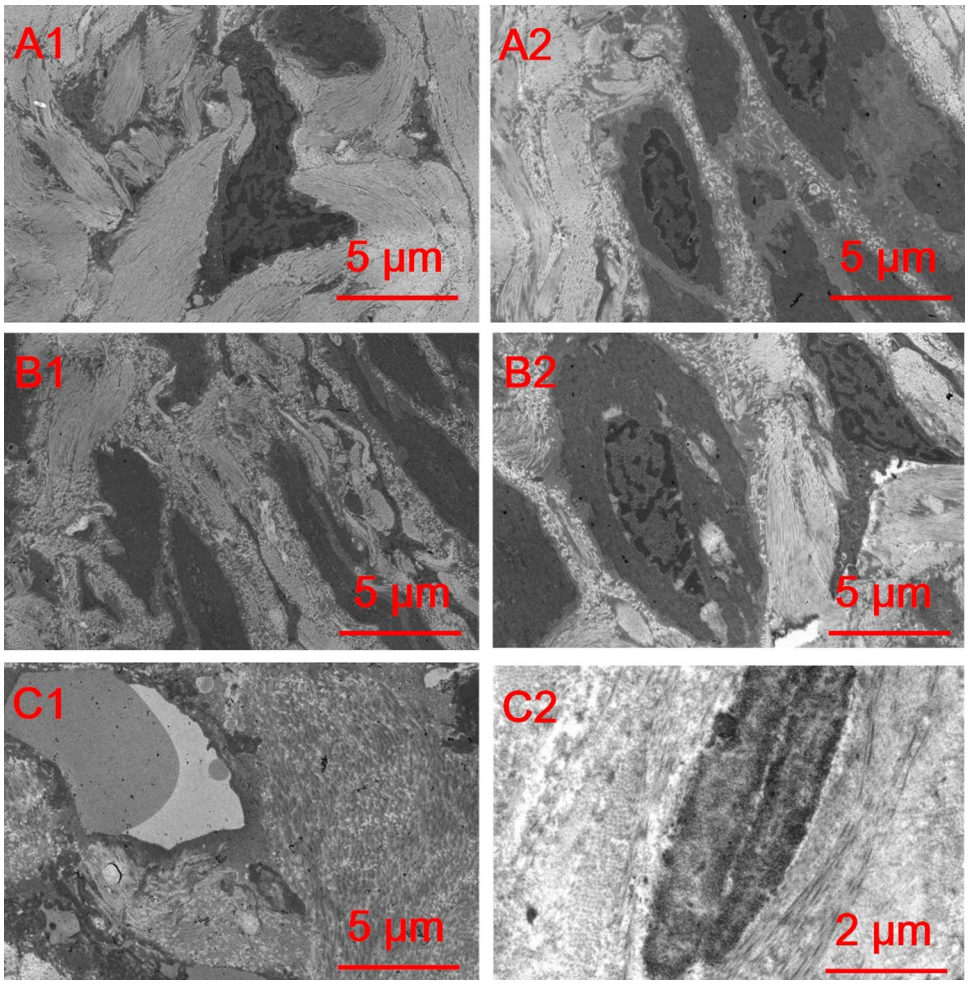

Fig. 5 Transmission electron microscope images showing morphological changes of basal tissues in the nipple areola flap before and after Intrabeam intraoperative radiotherapy. 30 min after removal of the mammary tissues (**a1, a2**), 60 min after removal of the mammary tissues (5 min before intraoperative radiotherapy) (**b1, b2**), 5 min after intraoperative radiotherapy (**c1, c2**)

Table 2 Radiation dose distributions of intraoperative radiotherapy measured by thermoluminescence materials ($n=5$)

Measuring sites	The ranges of minimum distance to the surface of spherical applicator (mm)	The ranges of actual radiation doses (Gy)[a]
Background signal (outside the operation room)	–[b]	7.091–10.590 ($\times 10^{-3}$)
Areola surface	3–5	8.894–11.063
Tip of nipple	10–16	2.121–3.304
Skin surface 2 cm away from the areola margin	–[b]	0.850–1.728
Surface of shielding material	18–25[c]	3.614–4.308
Space between shielding material and pectoralis major	19–26[c]	54.579–71.736 ($\times 10^{-3}$)

[a]Actual radiation dose = 16 × radiation dose measured at the target site/radiation dose measured at the surface of applicator

[b]Could not be measured precisely

[c](Distance at the end of expiration + distance at the end of inspiration)/2

Discussion

The NAC is excised simultaneously in conventional mastectomy. Although subsequent reconstruction of "NAC" or 3D tattoo technology can improve cosmetic outcomes to some extent, multiple surgeries are still needed [33, 34]. Postoperatively, the "NAC" does not look very natural and completely lacks sensation; both of these factors influence the psychological outcome [35, 36]. Many recent single-arm studies with large sample sizes [2–4, 8–11, 24] have shown that even when the NAC is not specially treated, the oncologic safety of NSM is good. Yet, how to manage the possible clinically and pathologically undetected residual

latent tumor in a retained NAC flap after NSM is still problematic. The most important characteristic of IORT is the high, single-fraction radiation dose for the small, effective irradiation target volume. IORT to the NAC may contribute to improving the oncologic safety of NSM. In this study we: (1) investigated the oncologic outcomes of Intrabeam IORT during NSM combined with breast reconstruction; (2) evaluated IORT-induced acute and chronic radiation injury; (3) investigated morphological changes in normal tissues after IORT, and (4) measured radiation dose distributions of IORT.

Simplicity of IORT and NAC complications

In this study, it took only about 30 min from installing to uninstalling the applicator, including administering the irradiation (usually < 14 min). The partial necrosis rate and total necrosis rate of the NAC were 7.3% and 0%, which is in line with the results of the ELIOT study (Novac-7 IORT) [30] and some studies [10, 37, 38] in which the NAC was not irradiated when applying NSM. Additionally, in the ELIOT study [30] and our study (Intrabeam IORT), it was found that although the cosmetic appearance of the NAC after NSM was good, sensation was significantly impaired. In our study, more than 90% of patients reported "no or poor sensation" of the NAC postoperatively. Furthermore, both HE staining and TEM imaging revealed morphological changes immediately after IORT in some normal tissues deep to the NAC flap. Surgery and radiation injury of the NAC flap are definitely associated with NAC postoperative complications (flap stasis, necrosis, skin traction, and hypesthesia, and the like).

Oncologic outcomes

In this study, almost half of the patients were less than 40 years old and 71% of the patients had Stage II/III disease. On the basis of our previous study [31], we expanded the surgical indications. Patients with lesions beneath the NAC were enrolled (but at least 2 cm away from the NAC skin according to mammography or MRI in a prone position, and/or at least 1 cm away from it according to sonography); these patients comprised 20% of the study cohort. The median duration of follow-up was 26 months. Except a breast-cancer mortality that occurred in one case, no recurrences or metastases were detected. The patient who died was young and had presented with triple-negative breast cancer. She had no abnormalities in the affected breast (including NAC) or chest wall by physical and imaging examinations 3 months prior to death.

Additionally, postoperative examinations of paraffin-fixed sections revealed DCIS in the residual NAC flap in two patients. Their breast tumors were invasive ductal carcinoma and DCIS, respectively. After Intrabeam IORTs to the NACs, no local treatment was undertaken in these two patients. After 20 and 24 months' follow-up, neither had evidence of recurrence or metastasis. Postoperative pathological examination reportedly resulted in identification of cancer cells in 5.1% of the NAC basal tissues in another study [39]. In that study, some patients (three with DCIS and five with invasive carcinoma in the NAC basal tissues) chose to receive postoperative EBRT to preserve the NAC. Their median follow-up period was 22 months, and none developed recurrence in the NAC skin.

Radiation dose distributions and IORT-induced radiation injury

In contrast with conventional small dose fractional EBRT, IORT involves a single large-dose of irradiation during surgery. We were, therefore, able to measure the radiation doses at different sites of the body, even at the surface of pectoralis major. The dose attenuation curve calculated by Intrabeam computer indicated that the radiation dose had attenuated to about 1/10 of the original value after the radioactive ray passing through 20-mm-thick tissues [31]. According to CT/MRI scan, the thickness of pectoralis + rib/intercostal muscle was between 10 and 20 mm in most cases in our study. What is more, by taking measurements at different sites in terms of thermoluminescence materials, we found that the radiation doses at the basal tissues of NAC flap (including ducts and possible residual gland tissues) were very high, and it was also relatively high at the areola surface, whereas the radiation dose at the skin surface outside the NAC, particularly > 2 cm from its margin, was very low. The radiation dose at the pectoralis major surface was low. And if a piece of shielding material (tungsten-filled polyurethane) was used, the radiation dose at the pectoralis major surface was small enough to be ignored. Additionally, after excluding the effects of chemotherapy and postoperative EBRT, we found no evidence of IORT-induced acute or chronic radiation injury to the lung, heart, or bone marrow. In short, Intrabeam IORT associated with NSM delivers high radiation doses to the irradiation target tissues (NAC flap), but very low radiation doses to the viscera.

Limitations of this study include that it was a small single-arm study, and the follow-up time was not long enough. It is yet to be determined whether decreasing the radiation dose would reduce the severity of loss of sensation in the NAC and/or the NAC necrosis rate without decreasing the oncological safety. It is also yet to be determined whether IORT associated with NSM should be limited to patients with high risk of tumor involvement in the NAC flap. Another question yet to be answered is how to treat patients in whom only postoperative pathologic examination

reveals residual cancer cells in the basal tissues of NAC flap. Is administration of IORT to the NAC flap combined with systemic treatments postoperatively adequate or should these patients' NACs be resected? All of these are our future research directions.

Conclusions

In the selected breast cancer patients, employing Intrabeam IORT-associated NSM combined with breast reconstruction may be safe and feasible. With the development of IORT, there will be wider application prospects of the technology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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