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Original Article

Intraoperative radiation therapy delivered prior to lumpectomy for early-stage breast cancer: a single institution study

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Abstract: Objective: To evaluate the safety, cosmesis, and clinical outcome of intraoperative electron radiation therapy (IOERT) delivered prior to lumpectomy for early-stage breast cancer. Methods: From December 2008 to March 2012, 75 breast cancer patients (ages 34-66 years) were treated with IOERT during breast conservative surgery. IOERT was delivered using a mobile linear accelerator. Suitable energy and applicator size were chosen to ensure coverage of the tumor with anterior and posterior margins of 1 cm and lateral margins of 2 cm. Patients with sentinel node metastases or younger than 40 years received 8 Gy as boost followed by post-operative external beam radiation therapy of 50 Gy/25F; the others had 15 Gy, prescribed to the 90% isodose depth. Adjuvant treatment consisted of chemotherapy (55 patients), hormonal therapy (59 patients), or combined chemotherapy and hormonal therapy (41 patients). The safety, cosmesis, and short-term outcome were evaluated. Results: Median follow-up was 54 months (range: 30-66 months). Two (2.7%) patients developed post-surgical hematoma. Six (8.0%) patients developed mild breast fibrosis. Eight (10.7%) patients suffered from local pain. One (1.2%) patient experienced a post-operative infection. Sixteen (21.3%) patients developed Grade 1 pulmonary fibrosis. Forty-three (57.3%) patients had an excellent cosmetic result and 23 (30.7%) had a good cosmetic result. Three patients had an ipsilateral breast recurrence, with an actual 3-year local recurrence rate of 4.0%. One patient had an ipsilateral axillary recurrence, resulting in a 3-year regional recurrence rate of 1.3%. No distant metastases or deaths were observed. The 3-year disease free survival was 94.6%. Conclusions: Intraoperative electron radiation therapy delivered prior to lumpectomy is safe and feasible for selected patients with early-stage breast cancer. Early side effects, cosmesis and short-term efficacy are acceptable, but a longer follow-up is needed for evaluation of late side effects and long-term outcome.

Keywords: Intraoperative radiotherapy, intraoperative electron radiation therapy, breast cancer, IOERT, whole breast radiation therapy

Introduction

Breast-conserving surgery (BCS) followed by whole-breast external-beam radiation therapy (WBRT) is one of the standard treatments for patients with early breast cancer. Multiple randomized trials have demonstrated the equivalence of breast-conserving therapy (BCT) to mastectomy in terms of local control and overall survival [1, 2]. Conventional post-operative adjuvant WBRT includes the whole breast to a total dose of 50 Gy in 2 Gy daily fractions over 5 weeks and a boost of 10 to 16 Gy to the tumor bed [3]. Although WBRT after surgery is able to improve local control, it also carries a number of disadvantages: 1) Side effects from whole-breast irradiation include potential radiation injury to organs at risk, such as lung and heart, and atrophy of the irradiated breast. For some patients, these side effects can outweigh breast preservation and the long-term oncological benefit from post-operative radiotherapy. 2) Post-operative WBRT takes 5~6 weeks, and can increase both healthcare costs and incon-

Table 1. Methods of intraoperative electron radiation therapy

IOERT	Number of patients	%
Energy		
6 MeV	19	25.3
9 MeV	31	41.3
12 MeV	25	33.4
Dose		
8 Gy	18	24.0
15 Gy	57	76.0
Applicator		
4.5 cm	1	1.3
5 cm	10	13.3
5.5 cm	25	33.3
6 cm	26	34.7
6.5 cm	13	17.4

IOERT, intraoperative electron radiation therapy.

venience for patients. 3) The sequence of chemotherapy and radiation therapy after surgery is still controversial. Delayed radiation therapy may contribute to a worse outcome.

Several studies have demonstrated that local recurrences after BCT are confined mostly to the same quadrant as the primary cancer [4, 5]. Accelerated partial breast irradiation (APBI), which aims to irradiate a portion of breast at a higher dose per fraction over a shorter time frame, has shown adequate local control, minimal toxicity, good cosmesis and become the object of scientific interest [6-8]. Intraoperative radiation therapy (IORT) is an APBI method that delivers a single high dose to the target volume during the operation and allows normal tissues to be better protected [9]. We started our Intraoperative electron radiation therapy (IOERT) breast program in August 2008. The aim of this study was to evaluate the efficacy of IOERT in terms of local control, side effects and cosmesis. To the best of our knowledge, this is the largest series of IOERT for breast cancer reported in the Chinese population.

Materials and methods

Patient selection

Between December 2008 and March 2012, 75 female patients, with a median age of 45 years (range: 34-66 years), were treated with IOERT during breast-conserving surgery in Chinese PLA General Hospital. All patients had staging investigations including chest X-ray, bone scan, liver ultrasound and brain MRI to rule out metastatic disease at diagnosis. Each patient had biopsy-proven adenocarcinoma. Local evaluation consisted of mammography, breast ultrasound and breast MRI in order to ensure that the tumor was unifocal and had a diameter ≤ 3 cm. Treatments were performed according to the Helsinki declaration. Written informed consent was obtained from all of the patients.

Surgical method

All patients underwent intraoperative lymphatic mapping and sentinel lymphadenectomy using combined radiocolloid and isosulfan blue dye technique. In our study, 57 (76.0%) patients had a negative sentinel node and no axillary dissection was performed; 18 (24.0%) patients with sentinel node metastases received complete axillary dissection. Then, a curvilinear or radial incision was made on the skin over the mass. Skin and subcutaneous flaps were raised circumferentially all around the area in question to expose the tumor and allow adequate placement of the radiation applicator. After delivering IOERT, all patients underwent extensive resection of the tumor to achieve a free margin of at least 1.5-2 cm whilst maintaining a good cosmetic outcome. The specimen was processed and assessed according to standard pathologic procedures.

IOERT method

IOERT was delivered prior to lumpectomy, using a Mobetron (Intraop Medical, Sunnyvale, CA), which is a mobile, self-shielded linear accelerator. This machine produces electron beam energies ranging between 4 and 12 MeV. The radiation is delivered from the Mobetron to the tumor bed through an applicator attached to the surgical table. The sizes of applicators available for the Mobetron range from 3-10 cm in diameter, with ½ cm increments. Suitable energy and applicator size were chosen to ensure coverage of the tumor with anterior and posterior margins of 1 cm and lateral margins of 2 cm. Patients with sentinel node metastases or younger than 40 years received 8 Gy as boost followed by a post-operative external beam radiation therapy of 50 Gy/25F; the others had 15 Gy prescribed to the 90% isodose depth. After the applicator and the Mobetron were aligned, everyone leaved the operation room

Table 2. Patients' characteristics

Characteristics	Number of patients	%
Age (y)		
< 40	17	22.7
40~60	51	68.0
≥ 60	7	9.3
T Stage		
T1	56	74.7
T2	19	25.3
N Stage		
N0	57	76.0
N1	18	24.0
Histological type		
Invasive ductal carcinoma	68	90.7
Others	7	9.3
Grade		
I	10	13.3
II	37	49.4
III	18	24.0
Unknown	10	13.3
Markers		
ER+	60	86.7
PR+	56	74.7
HER2+	11	14.7
Triple Negative	5	6.7

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.

and anesthesia was monitored remotely. The dose rate was 10 Gy/min., which means treatment could be completed in 1-2 minutes. Parameters of the IOERT delivery are shown in **Table 1**.

Post-operative treatment

In our study, 18 patients who were given 8 Gy of IOERT as boost also had post-operative radiation therapy of 50 Gy in 25 fractions to whole breast +/-supraclavicular area. Adjuvant chemotherapy and endocrine therapy were prescribed according to the final pathologic characteristics. Fifty-five patients received chemotherapy, 59 received endocrine therapy, and 41 had combined chemotherapy and endocrine therapy.

Follow-up

Patients were evaluated for side effects, cosmesis and tumor control with history, physical examinations and breast ultrasound at 1, 3, 6, and 12 months after radiation therapy, and every 6 months thereafter. Acute and late side effects were evaluated according to Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) late morbidity Scoring Scale [10]. Cosmesis was scored by both physician and patient using the RTOG cosmesis rating system [11].

Statistical analyses

Local control and survival were analyzed by the Kaplan-Meier method to estimate survival functions. Statistical analyses were performed with IBM® SPSS® Statistics, version 20.

Results

From December 2008 to March 2012, 75 patients received IOERT. Till October 2014, median follow-up was 54 months (range: 30-66 months). Among them, 57 patients had 15 Gy of IORT alone, 18 patients had 8 Gy of IOERT as boost and post-operative whole breast (+/-supraclavicular area) radiation therapy of 50 Gy in 25 fractions. The tumor histology of 68 (90.7%) patients was invasive ductal carcinoma; the others included mucinous adenocarcinoma, metaplastic carcinoma, invasive tubular carcinoma, and apocrine carcinoma. Patient characteristics are shown in **Table 2**.

Side-effects

No patients developed acute hematologic toxicity. Two (2.7%) patients who received 15 Gy of IOERT developed postoperative haematoma. Six (8.0%) patients developed mild breast fibrosis. and 8 (10.7%) patients suffered from local pain. One (1.2%) patient experienced wound infection, Sixteen (28.1%) of the 57 patients receiving 15 Gy of IOERT alone developed Grade 1 pulmonary fibrosis 3-6 months after IOERT. The median wound healing time was 12 days (range, 10-14 days). No delayed healing was noted. There were no Grade 3 or 4 toxicities and no serious adverse events related to the IOERT.

Cosmesis

In this study, the cosmetic outcome of all patients was reasonable with excellent or good results in more than 85% of patients. Torty-

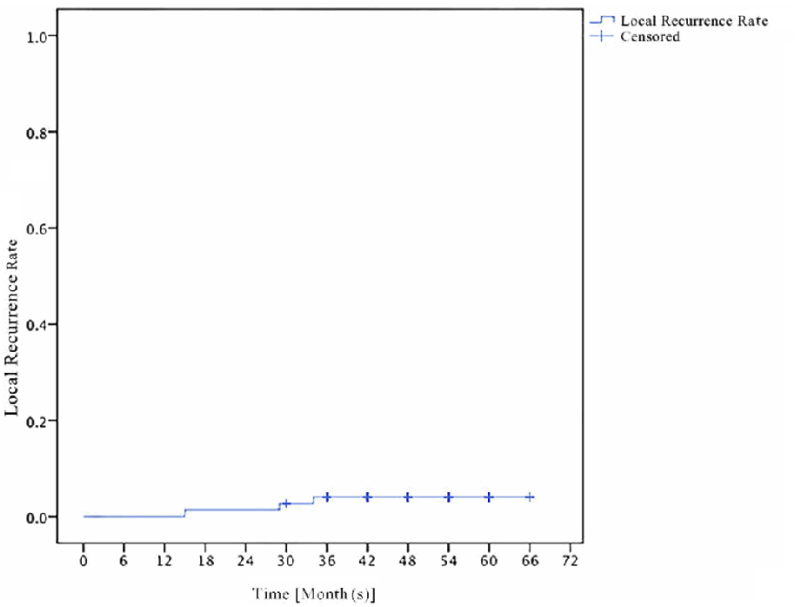

Figure 1. Recurrences occurred in 4 (5.3%) of 75 patients. Three patients had ipsilateral local tumor recurrences 15, 29, and 34 months after IOERT, respectively. Actual 3-year local recurrence rate was 4.0%, or conversely actual 3-year local control rate was 96.0%.

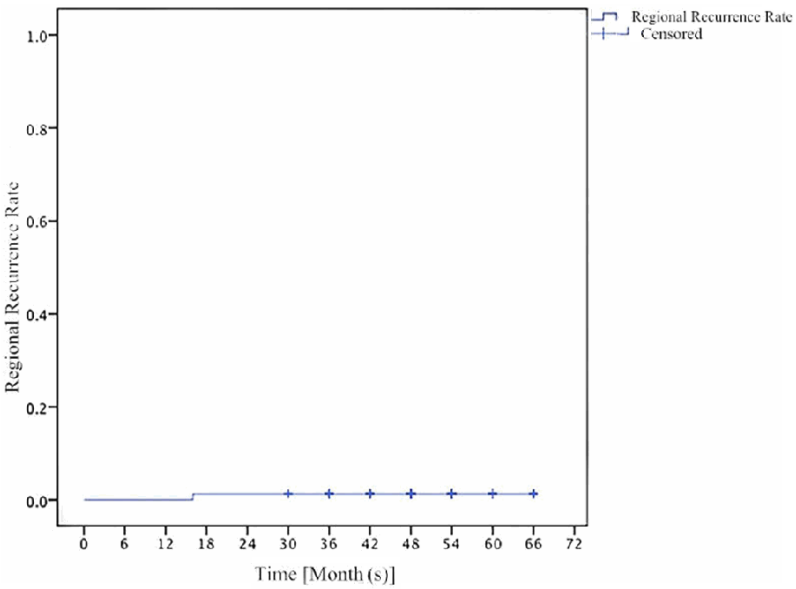

Figure 2. One patient had ipsilateral axillary recurrence 16 months after IOERT, resulting in a 3-year regional recurrence rate of 1.3%.

three (57.3%) patients had an excellent cosmesis and 23 (30.7%) had a good cosmesis; 8 (10.7%) were evaluated as fair and 1 (1.3%) was evaluated as poor.

Local control

Recurrences occurred in 4 (5.3%) of 75 patients. Three patients had ipsilateral local tumor recurrences 15, 29, and 34 months after IOERT, respectively. Actual 3-year local recurrence rate was 4.0%, or conversely actual 3-year local control rate was 96.0% (**Figure 1**). One patient had ipsilateral axillary recurrence 16 months after IOERT, resulting in a 3-year regional recurrence rate of 1.3% (**Figure 2**). All of the 4 recurrent patients underwent mastectomy, and were disease free at last follow-up. The 3-year disease free survival was 94.6% (**Figure 3**). All the 4 recurrent patients had some unfavorable factors, such as young age, tumor size greater than 2 cm, grade III tumor, HER2 positive, ER negative or triple negative tumors. Three of them underwent IOERT alone and one of them underwent WBRT following IOERT as a boost. Two recurrent patients with human epidermal growth factor receptor 2 (HER2) positive tumors were not treated with trastuzumab due to their personal choice. Characteristics of tumor recurrences are shown in **Table 3**. No distant metastases or cancer-related deaths were observed.

Discussion

In recent years, APBI has gradually become of increasing clinical interest. Clinical trials have demonstrated that APBI offers equivalent survival, comparable local control and improved cosmesis compared to WBRT. As one of the APBI techniques, IOERT is more accurate and able to protect normal tissues better compared to WBRT. IOERT delivers a highly effective biological dose to the tumor in a single fraction, so, when used as a boost, it can inhibit the proliferation of tumor cells during the time interval between

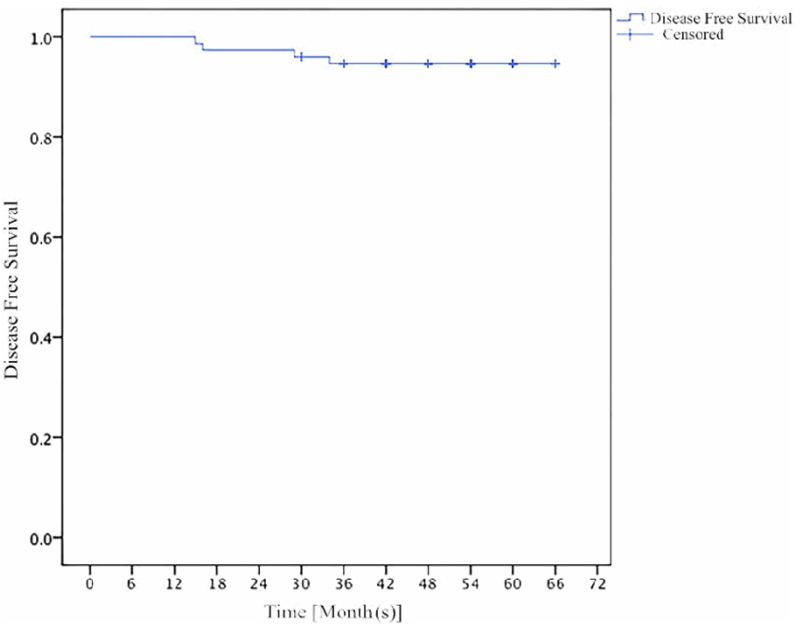

Figure 3. All of the 4 recurrent patients underwent mastectomy, and were disease free at last follow-up. The 3-year disease free survival was 94.6%.

surgery and adjuvant WBRT and also during the fractionated WBRT. IOERT also shortens the treatment time, which is more convenient for patients and reduces the relevant cost of treatment. Over the last decade, the use of IOERT in breast cancer has steadily increased. More and more studies have suggested that IOERT APBI could be a new treatment choice for selected low-risk patients with early-stage breast cancer, and may be able to completely replace WBRT after surgery [12, 13].

IOERT can also be used as a replacement for the external beam boost portion, which delivers 10-16 Gy to the tumor bed, following 50 Gy adjuvant WBRT [14, 15]. When performing external beam boost, the delineation of the tumor bed often depends on imaging the residual seroma in the cavity that remains after resection, and/or imaging the metallic clips placed by surgeons around the cavity during the operation, as imaged during CT treatment planning. Delineation of the tumor bed even with these imaging markers can vary from doctor to doctor, thus affecting the external beam boost accuracy, as well patient breathing and the inter-fraction variation of the imaged tumor bed. The advantage of IOERT is that the target volume can be directly visualized and irradiated accurately, while avoiding excessive irradiation of normal tissues and skin. IOERT as a boost also reduces the post-operative radiation time by 5-8 days. The first clinical study on IOERT as a boost was reported by Lemanski et al [15]. In their study, 50 early-stage breast cancer patients were treated with 10 Gy IORT followed by 50 Gy WBRT. They achieved a 10-year disease-free survival of 83% and 10-year overall survival of 94%. These patients had a very good quality of life and good to excellent cosmesis. Fastner et al. [16] reported a pooled analysis of 1110 patients treated with IOERT boost. After a median follow-up of 72.4 months, 16 local recurrences were observed. The 7-year local control rate was 99.2% and the 7-year overall survival was 90%. Taking into account patient age, annual in-breast recurrence rates were 0.64%, 0.34%, 0.21% and 0.16% in patients < 40 years, 40-49 years, 50-59 years and ≥ 60 years, respectively. The authors state that these results compare favorably to the best reported rates in all age groups using external beam boost.

IOERT can be delivered as a single fraction dose of 15-21 Gy to replace the entire course of WBRT. There is not yet an established standard method or dosage used to deliver IOERT APBI. Some deliver the IOERT pre-lumpectomy, and some post-lumpectomy, and the dose can be prescribed to the 80% isodose or the 90% isodose. All the APBI approaches claim biologic equivalence to the standard WBRT approach. The most widely used technique is that proposed by the European Institute of Oncology (EIO) in Milan by Veronesi [17, 18]. In this approach, patients are treated by IORT with electrons alone (ELIOT) with a single dose of 21 Gy to the 90% isodose immediately after quandrantectomy. The excision cavity is temporarily re-approximated to accommodate the placement of the electron applicator, and the chest wall is protected with a metallic disk.

The EIO [19] reported the results of 1822 non-randomized patients receiving ELIOT. With a median follow-up of 36 months, 2.3% of the

Table 3. Characteristics of the patients who had tumor recurrences

Patient	Age (y)	Tumor size (cm)	ER	PR	HER2	Grade	Chemo-therapy	Endocrine therapy	IOERT	WBRT
1	57	1.5	+	+	+	III	Yes	Yes	15 Gy	No
2	55	3	-	-	+	III	Yes	No	15 Gy	No
3	36	2	-	-	-	II	Yes	No	8 Gy	50 Gy
4	42	2	-	-	-	III	Yes	No	15 Gy	No

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; IOERT, intraoperative electron radiation therapy; WBRT, whole breast radiation therapy.

patients developed a local recurrence, 1.3% a new primary ipsilateral carcinoma and 1.4% distant metastases as a first event. Five- and ten-year overall survivals were 97.4% and 89.7% respectively. Local side effects of ELIOT were mainly liponecrosis (4.2%) and fibrosis (1.8%). Leonardi et al [20, 21] subsequently analyzed these patients compared to ASTRO and ESTRO guidelines for APBI patients. For ASTRO suitable, cautionary and unsuitable patients, they found 5-year Kaplan-Meier projections for recurrence of 1.5%, 4.4% and 8.8%, respectively. For ESTRO good, possible and contraindicated patients, the 5-year projections for recurrences were 1.8%, 7.4% and 7.8%, respectively.

Veronesi et al [22] reported on a randomized ELIOT Trial which closed on December 2007, with 1305 patients randomized: 651 to ELIOT, and 654 to EBRT which consisted of 50 Gy of WBRT plus a 10 Gy boost. The ELIOT and EBRT patients achieved 5-year recurrence rates of 4.4% and 0.4%, respectively ($P < 0.0001$), with a median follow-up of more than 5.5 years. When analyzing for risk of relapse, the 5-year ipsilateral breast tumor recurrence (IBTR) exceeded 10% for patients who had tumors > 2 cm (10/83 = 10.9%), 4 or more positive nodes (4/31 = 15.0%), or those with poorly differentiated tumors, i.e. grade III (15/129 = 11.9%), or with ER-tumors (8/63 = 14.9%), or with triple negative disease (7/43 = 18.9%). The 5-year IBTR was 11.3% for the 199 (30.6%) patirents with one or more of these risk factors, vs. only 1.5% for the remaining 452 (69.4%) patients who had none of these factors (ELIOT low risk). The ELIOT arm had less skin damage (i.e. erythema, dryness, hyper-pigmentation, or itching) than the conventional arm ($P = 0.0002$). There were no differences in fibrosis, retraction, pain or burning, but there was a higher incidence of radiological determined fat necrosis in the ELIOT group, 5%, vs. 2% for the EBRT group ($P = 0.04$). In addition, ELIOT showed less pulmonary toxicity than the EBRT arm [23] as diagnosed by follow-up spiral CT (4 in the ELIOT arm and 38 in the EBRT arm). These differences in skin and pulmonary toxicities are not unexpected given the differences in IOERT vs. EBRT radiation techniques. The authors point out that less skin damage through use of IOERT might be important in the event of a salvage mastectomy for recurrence. The integrity of the skin, they say, is important to the success of skin sparing and nipple sparing mastectomies, which are rapidly becoming standard procedure.

In another phase II IOERT APBI study of 226 carefully selected low-risk 226 patients, Maluta et al [24] had only one recurrence with a mean follow-up of 46 months. The initial patients were women > 50 years with biopsy proven invasive ductal carcinoma, who had grade I and grade II tumors < 2 cm, and were N0, ER+ and PR+. When ESTRO/ASTRO released their guidelines for APBI suitable and good patients, they expanded inclusion criteria to be consistent with these recommendations. All patients still had quandrantectomy and axillary node management, including sentinel node evaluation and completion of axillary node dissection for positive sentinel nodes, but the radiation technique was modified from the ELIOT approach. The prescribed dose was reduced by about 10%, so the maximum dose to the tumor was 21 Gy with the energy selected to assure that the entire target was covered to at least the 80% dose line. Using the linear-quadratic model, both dose regimens gave an adequate dose for tumor control when compared to 6 weeks of EBRT. With a mean follow-up of 46 months, only one recurrence in a quadrant outside the index quadrant was observed. The treatment toxicity was very low, with only 15 patients experiencing various grade 1 complications (on the SOMA-Lent scale), and 1 patient experiencing grade 3 complications.

A Japanese phase I/II IOERT study by Sawaki et al [25, 26] demonstrated the safety and feasibility of a single dose of 21 Gy in Asian breast cancer patients when the radiation was delivered immediately after the surgical excision of the tumor.

The University of North Carolina was the first reported center to deliver IOERT to the tumor prior to surgical excision, as we did. They thought the delivering IOERT before excision allowed better tumor localization and more uniform dose distribution in the tumor and surrounding tissues [27, 28]. However, the results of their study on the 53 patients who received IOERT alone showed 3-year, 5-year and 6-year local recurrence rates of 8%, 13% and 15%, respectively. This is notably higher than other clinical APBI studies [28], but only one of the 22 ASTRO suitable patients in their study recurred. The researchers explained their high local recurrence rates by under-estimation of the intraoperative tumor margins due to delivering IOERT prior to excision and a lower prescription dose.

Our trial used the same IOERT technique and prescription dose as the University of North Carolina. In our study, the toxicity of IOERT was low, without IOERT related grade 3-4 toxicities or serious adverse events. More than 85% of the patients had a good or excellent cosmesis, which was consistent with what others have reported. The 3-year overall recurrence rate was 5.3%, which was lower than the University of North Carolina, but higher than we had anticipated. The possible explanations are similar with that of University of North Carolina. Firstly, delivering IOERT prior to lumpectomy may underestimate the irradiated tumor margins. The field size was determined using pre-operative ultrasound and MRI, but the real tumor size could be larger because of the infiltrating characteristic of malignant tumors. Secondly, the dose of 15 Gy may be inadequate as discussed previously. Thus, local recurrence could be decreased if we enlarge the irradiated tumor margin and increased the delivered dose. Thirdly, patient selection for IOERT APBI is critical as well. Patients with unfavorable factors, classified as cautionary or unsuitable for APBI by ASTRO have been shown to have a substantially higher risk for recurrence [29, 30]. It is clear from maturing IOERT APBI studies, that ASTRO suitable or ELIOT low risk patients are the most favorable group. In our case, since lumpectomy was performed after IOERT, final pathologic characteristics were not known at the time of irradiation. In our approach, patients with metastatic sentinel nodes or younger than 40 years of age received 8 Gy of IOERT as boost followed by adjuvant WBRT; the others received 15 Gy of IOERT to replace the entire course of WBRT, even if the post-operative pathology results subsequently revealed aggressive tumor features. Among the 4 recurrent patients, all of them were younger than 60 years and 1 patient even younger than 40 years; two had triple negative (ER-, PR-, HER2-) tumors and two had HER2+ tumors; three had grade III tumors. Thus we propose adjuvant WBRT after IORT for the patients with unfavorable factors.

Conclusions

IOERT delivered prior to lumpectomy is safe and feasible for selected patients with early-stage breast cancer. Early side effects, cosmesis and short-term outcome are acceptable, but a longer follow-up is needed to evaluate late side effects and long-term outcome.

Disclosure of conflict of interest

None.

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