RESEARCH COMMUNICATION

Interoperative Radiotherapy of Seventy-two Cases of Early Breast Cancer Patients During Breast-conserving Surgery

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Abstract

Objective: To evaluate interoperative radiotherapy after breast conservative surgery in early breast cancer patients in terms of postoperative complications, cosmetic outcome and recurrence events. Methods: From June 2007 to Dec 2011, 143 early breast cancer patients received breast conservative surgery. Seventy-two (study group) received interoperative radiotherapy, compared with 71 patients (control group) given routine radiotherapy. Postoperative complications were evaluated 1 month after surgery; cosmetic outcome was evaluated 1 year postoperatively; recurrence and death events were followed up. Results: The average wound healing time was 13~22 d in the study group and 9~14 d in the control group. In the study group, 2 patients developed lyponecrosis, 16 patients showed wound edema while no such side effects were found in the control group. No infection or hematomas were found in either group. In the study group (59 cases), overall cosmetic outcome in 53 patients was graded as excellent or good, and in 6 as fair or poor. Meanwhile in the control group (56 cases), 42 patients were graded as excellent or good, and 14 as fair or poor (*P*=0.032). After a follow-up from 3 to 54 months (median: 32 months), two patients (2.78%) in study group developed local relapses, one of them (1.39%) died, 2 patients (2.78%) developed bone metastases. In control group, one patient (1.41%) developed local relapse, 2 patients (2.82%) developed bone metastases, and no one died. Conclusion: Intraoperative radiotherapy is safe and reliable with good cosmetic outcome.

Keywords: Breast neoplasm - radiotherapy - breast conservative surgery

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Introduction

Whole breast radiotherapy after completion of chemotherapy in breast-conserving surgery (BCS) has become the standard treatment of early breast cancer (Fisher et al., 2002; Veronesi et al., 2002). In recent years, because of application of sentinel lymph node biopsy many patients are exempt from complications associated with lymph node dissection (Veronesi et al., 1997; Veronesi et al., 2001). Veronesi et al. (2001) found that 85% of recurrence after BCS occured in the scar area and they proposed that whether the whole breast radiotherapy after BCS could be replaced by partial radiotherapy only around the tumor bed. Since the end of the last century, many researches on partial breast irradiation therapy after BCS have been reported (Veronesi et al., 2003; Luini et al., 2005; Beal et al., 2007; Sawaki et al., 2009; Abbott et al., 2011). Intraoperative radiotherapy (IORT) is to deliver sufficient quantities of single irradiation only to the tumor bed after tumor resection surgery.

From June 2007 to Dec 2011, 143 cases of patients with early breast cancer underwent breast conservative surgery in our hospital: 72 cases underwent interoperative radiotherapy in study group and 71 cases underwent routine radiotherapy in control group. The effect of treatment by intra-operative radiotherapy is more satisfactory compared with the control group. The results are reported as follows.

Materials and Methods

Patients

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Fourth Peoples Hospital of Wuxi City. Written informed consent was obtained from all participants.

The patients enrolled were met on the following criteria: 1) Ages of the patients: ≥ 40 years old. The age limit can be relaxed in case of those patients with special type of cancer (such as mucinous adenocarcinoma) or tumor size (diameter: ≤ 1cm). 2) Tumor distance from the areola > 2 cm, tumor size ≤ 2.5 cm. 3) Multifocal cancer was excluded by preoperative mammography films, color B- scan ultrasonoscope or MRI examination. No obvious axillary lymph node enlargement was found

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through preoperative imaging and clinical examination. No contraindication for BCS such as history of chest radiation therapy or active connective tissue disease. 4) The patients can be closely cooperate with the treatment of chemotherapy, endocrine therapy, targeted therpy (Her2 positive). 5) After tumor removal druing intraoperative sugery, quick slice for the first time is required in the study group to obtain tumor-free cut edge each. 6) Patients were willing to accept the treatment and sign the special IORT consent. Patients whose number of axillary lymph node metastase is ≥ 4 detected by postoperative rountine pathological examination would withdraw from the study and treated with modified radical mastectomy and conventional radiotherapy.

Surgical method

Anesthesia: Continuous epidural anesthesia was adopted. The patients were willing to be monitored by image system. Surgical operation: According to the methods described by Mattia Intra and others (Intra et al., 2002), the tumor was as the center and the skin incision was curved or radial. If the breast tumor is close to skin, the skin surface and subcutaneous adipose tissue of the tumor should be removed. If the tumor is close to chest fascia, the skin should be reserved. The tumor bondary was marked by methylene blue. Outside from the margin (about 1 cm), loop excision of the tumor was operated deeply to the pectoralis major fascia. The resection specimens were labeled with "up, down, left, right and the skin lateral edge". Rapid histological examination of the specimen was done to determine whether the tumor was the invasive carcinoma and the cutting edge was clear. If the cutting edge was not clear, the patient had to be withdrawn from the study. Subsequently, curved incision had been done under the armpit for biopsy of sentinel lymph node or dissection of lymph node.

(1) Free of galactophore: In order to expose the target tissue for irradition, after the tumor was excised in experimental group, the galactophore was further free to tumor bed outside about 3-5 cm (Intra et al., 2006) . When the superficial surface of galactophore was separated from the subcutaneous fat layer, the flap blood supply should be carefully retained to avoid postoperative flap ischemic necrosis. (2) Protection of thoracic wall: In order to reduce expoure to the thoracic wall and ensure sufficient quantities of irradiation to the target of galactophore, a round or oval-shaped lead sheet (thickness: 3 mm, diameter: 8-10 cm) swathed in gauze and plastic film was placed between the free galactophore and chest muscle. The lead disc should be bigger than the size of the target tissue. (3) Suture of galactophore: the interrupted full thickness sutures of the galactophore in front of the lead piece should be uniform to ensure the homogeneity of the irradiation target and to receive the best dose distribution within the gland. The first and last stitches were sewn on plastic film wrapped in lead plate to avoid moving of lead plate during operation. A pin was inserted into the target gland and was touched to the lead plate to measure the gland thickness for selection of the e-ray energy (Mev).

Implementation of IORT

Selection, placement of applicator used for IORT and link to accelerator: The material of applicator equipment used for IORT was round (diameter: 6, 8, 10 cm) or oval (specification: 4×6 cm, 6×8 cm) polymethyl methacrylate. Its contact surface to breast was flat or beveled. The applicator was inserted through the skin incision and directly contact with the target breast. Accurate placement of the cylinder was the guarantee of radiation to cover the entire target area. The center of the cylinder was fixed to the center of the previous staining part of breast surface and the applicator should cover the cutting edge of the foci more than 2-3 cm. When the cylinder was properly placed the applicator was docked to the accelerator.

The linear accelerator we used was Varian Clinic 23EX. The curve was drawn according to the obtained values of percent depth dose (PDD) of electronic accelerator after application of the cylinder (Figure 1). In order to ensure more than 90% of irradiation dose reach to the target area of breast surface and deep sides, saline gauze with 2-5mm of thickness as a tissue equivalent filler was placed on the irradiated target area of breast surface. According to the determined thickness of the breast target, 9 or 12 MeV of electronic line was selected and the prescription dose of target area was 21 Gy (the biological effect is equivalent to 58-60 Gy of conventional fractionated irradiation) by a single irradiation for about 3-5 min of duration.

After radiotherapy, withdraw the applicator from the incision, remove the breast sutures and the lead sheet, set the Pan's drainage and suture breast and skin finnally. Antibiotics were used for prevention of postoperative infections.

Dose monitoring: IVD Solution micro-probe was placed for determination of radiation dose. Placement sites: (1) Front and back (front of lead plate) of the center and edge of the target breast; (2) Back of lead plate (front of pectoralis major muscle); (3) Outside of the applicator (1, 5 and 15 cm) (Veronesi et al., 2001; 2003).

Study items

1) The actual target dose. Whether the doses of pectoral surface and outside of the applicator (1, 5 and 15 cm) were safe. 2) Postoperative complications of IORT: Whether incision dehiscence, edema effusion, infection, hematoma, fat necrosis and liquefaction may occur after operation for a month. 3) Cosmetic evaluation of breast appearance by JCRT standard (Dubois et al., 1997). The evaluators include the surgery group, plastic surgery and radiation oncology doctors. 4) Tumor recurrence or death events.

Statistical analysis

The Software SPSS 13.0 was used for statistical analysis with the Student's t-test. Data with a P value of less than 0.05 were considered significant.

Results

Clinical data

The detailed clinical data are shown in Table 1.

Irradiation doses

The doses in 66 cases of targeted breast with thickness from 1.4 to 3.0 cm were 20-21 Gy. The doses in 6 cases of

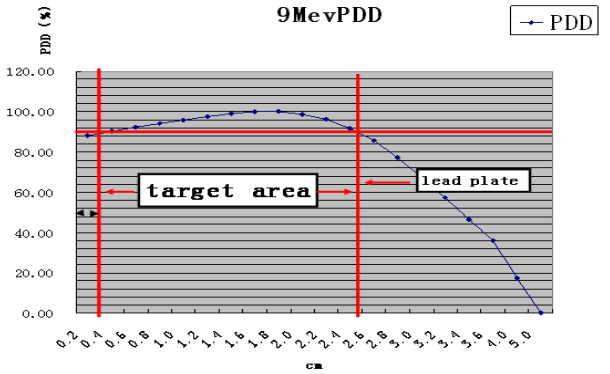

Figure 1. The Percent Depth Dose (PDD) Curve of the Electron Accelerator After Application of the Applicator

targeted breast with thickness above 3.0 cm were19-20 Gy. The doses of pectoral surface and outside of the applicator with different distances were lower than 0.1 cGy.

Wound healing time

The average wound healing time in study group is 13-22 d and 9-14 d in control group. In the study group, fat deliquescence occurred in 2 patients and wound edema occurred in 16 patients but no lyponecrosis and wound edema were found in control group. No infection or hematomas were found in the two groups.

Cosmetic evaluation of postoperative breast appearance

Overall cosmetic outcome was rated after post operation for 1 year. 53 of 59 cases in the study group were graded as excellent or good, 6 patients were as fair or poor. Meanwhile in the control group (56 cases), 42 patients were grade as excellent or good, 14 patients were as fair or poor (P=0.032).

Follow-up

In the present study, after a follow-up from 3 to 54 months (median, 32 months), three cases of patients underwent sugery again in study group. According to the patient's firm demand one case of patient underwent total mastectomy and no carcinogenesis was found in the resection specimen. Two patients (2.78%) in study group developed local relapses. No armpit lymph node was found in one case of patient through preoperative physical examination, ultrasonography and mammography. However, four pieces of lymph node metastasis were found through postoperative pathologic examination. Therefore, this patient was informed the pathway withdrawn from the study and continued to be treated with modified radical cure and postoperative radiotherapy. Unfortunately, due to the patient's uncooperation, total mastectomy and radiotherapy had been performed until local recurrence occurred 10 months after postoperation. At present, lung metastasis was found. Tumor immunohistochemical HER2 in one case of patient was showed (+++) and the patient was further diagnosed by FISH as HER-2 positive breast cancer. The patient did not cooperate to do chemotherapy and was unwilling to be treated with targeted therapy. The patient underwent modified radical cure as local recurrence happened 12 months after postoperation and died of systemic metastases 26 months later. In study group, bone metastasis was found in 2 cases of patients (2.78%) 24 and 31 months after operation. In control group, one patient (1.41%) developed local relapse, 2 patients (2.82%) developed bone metastases, and no death occurred.

Table 1. Clinical Pathological Factors

Clinical Pathological Factors	Experimental group	Control group
Age		
31~39	15	13
40~49	27	27
50~59	21	19
≥60	9	12
Tumor position		
upper outer quadrant	45	47
lower outer quadrant	15	14
upper inter quadrant	8	7
lower inter quadrant	4	3
Tumor maximum diameter		
<5mm	6	5
5~9mm	11	10
10~15mm	30	30
16~20mm	18	20
>20mm	7	6
Histological Examination		
Invasive ductal carcinoma	55	55
Invasive lobular carcinoma	4	4
Mucinous adenocarcinoma	5	4
Intraductal carcinoma micrometastasis	8	7
Medullary carcinoma	0	1
Lymph node metastasis (pathology)		
N0	72	66
N1	7	6
N2	1*	0
Immunohistochemistry		
ER+/ and/or/PR+	39	28
ER- andPR-	32	32
Her-2+(Fish)	4	3
Chemotherapy	72	71
Targeted therapy **	3	3

*One patient withdrew from the study; **Herceptin treatment for one year

Discussion

After a BCS, patient with early breast cancer often undergo chemotherapy and whole breast radiotherapy for 5-7 weeks. However, there always exist atrophy of the irradiated breast, rough skin and pigmentation in some patients treated by whole breast radiotherapy. Appearance of the conserving breast is often less than desirable. Thus these results triggered researches whether it is necessary to undergo the whole breast radiotherapy after BCS. The resluts of follow-up of 12 years after BCS reported by Veronesi et al showed that 85% of local recurrence occurred in the surgical area and the remaining 15% in the different quadrants out of the surgical area. The results of a small-scale radiation research performed by Ribeiro et al. (1993) indicated that the rate of local recurrence after small range of radiotherapy slightly increased. The main local recurrence was invasive lobular carcinoma. There were no differences on survival rate. Results of other

studies (Perera et al., 1997; Vicini et al., 1999) also showed that the local control rate of local radiotherapy after BCS was 92-100%. Therefore, research on IORT after BCS increased gradually in recent years. The advantages are listed as follows: (1) Accurate location of the targeted radiotherapy region and direct irradiation to the high risk of recurrence of breast; (2) To avoid the vital organs (lung, heart, etc) to be irradiated, and to reduce radiation injury and occurrence of the second primary induced by radiation; (3) Application of single high dose of irradiation may improve the radiation biological effects. 21GY of a single dose of irradiation in surgery has equivalent effect to 58-60 GY of conventional radiotherapy; (4) Shortening the interval of surgery and radiotherapy. (5) To effectively resolve the patients' problems of round trip to the radiotherapy center; (6) Because of irradiation by IORT only to small partial breast some adverse effects including atrophy of the irradiated breast, rough skin and pigmentation can be avoided after the whole breast radiotherapy. Further more, it has good cosmetic effect which is also the original intention of BCS.

IORT has been carried out in our center since June 2007. The linear accelerator we used in the present study was Varian Clinic 23EX. The percent depth dose (PDD) of the electron accelerator will change when the applicator was used. Therefore, we determined the PDD values of 9Mev and 12Mev using different types of applicators. According to the determined values and the thickness of the breast target, 9 or 12 MeV of electronic line was selected. Saline gauze with 2-5mm of thickness as a tissue equivalent filler was placed on the irradiated target area. According to the optimal parameters, the determined values of doses after irradiation were: The doses in 66 cases of targeted breast with thickness from 1.4 to 3.0 cm were 20-21 Gy. The doses in 6 cases of targeted breast with thickness above 3.0 cm were19-20 Gy. The doses of pectoral surface and outside of the applicator with different distances were lower than 0.1 cGy. The results demonstrated that application of IORT carried out in our center is safe and reliable not needing to worry about the irradiation injury to lung, heart, skin and the counter side of breast.

IORT has fewer complications. According to the results reported by Veronesi et al. (2005), complications were found only in 38 (6.3%) of 590 cases of patients, which included: severe fibrosis in 1 case (0.2%), mild fibrosis in 18 cases (3%), fat necrosis in 15 cases (2.5%), hematoma in 2 cases (0.3%), shrinking skins in 2 cases (0.3%). In the present study, of the 72 cases of patients, wound fat liquefaction in 2 cases and incision edema for 5-7 days and more fluid of drainage in 16 cases were found. Since 2009, we have paid more attention to breast superficial surface without adipose tissue as much as possible when the breast gland was separated. Thus, fat liquefaction necrosis after irradiation may be avoided and rare complication occurred.

Adverse factors including breast atrophy, rough skin and pigmentation can be avoided through application of IORT. These adverse factors may be caused by the whole breast irradiation. At the same time, because the breast gland was fully separated during the operation, the skin and breast can be sutured with no tension. Therefore, cosmetic effect of IORT is better than that of the whole breast irradiation. Considering cosmetic effect may be affected after the recent surgery and radiotherapy and usually the patient can be in stable one year after surgery, the cosmetic effect in the present study was evaluated one year after operation. The results indicated that the ratios of excellent or good effect in the study group were better than those in the control (P=0.032).

The rate of local control by IORT after BCS was high. As reported by Veronesi et al. (2005), After a follow-up from 4 to 57 months (mean, 24 months; median, 20 months), of 590 cases of patients, three patients (0.5%) developed local recurrences, 3 patients ipsilateral carcinomas in other quadrants and other 5 patients contralateral breast carcinoma. One patient (0.2%) died of distant metastases. In the present study, after a follow-up (median, 32 months), of 72 cases of patients, two patients developed local recurrences. However, no armpit lymph node was found in one of the two patients through preoperative physical examination, ultrasonography and mammography. Unfortunatelly, four pieces of lymph node metastasis were found through postoperative pathologic examination. Therefore, this patient was informed the pathway withdrawn from the study and continued to be treated with modified radical cure and radiotherapy after operation. One case of patient was diagnosed as HER-2 positive breast cancer. The patient was unwilling to accept chemotherapy and be treated with Trastuzumab mAbs. Actually, t

The two cases have been told to quit IORT. Recurrence may be related to the patients' uncooperation with the treatment, but not to IORT itself. Sixty-nine cases of the follow- up patients met the inclusion criteria have not been found local recurrence so far. Therefore, as long as strict indications are applied, satisfactory rate of local control can be guaranteed.

In summary, we carried out IORT after BCS of breast cancer in 72 cases of patients. The preliminary results of 54-month follow up suggested that IORT is safe, reliable with good cosmetic outcome and satisfactory tumor local control, which is worthy of further investigation.

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