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Intraoperative radiotherapy given as a boost after breast-conserving surgery in breast cancer patients

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Abstract

Conventional radiotherapy after breast-conserving therapy is confined to 50–55 Gy external beam radiation therapy (EBRT) to the whole breast and 10–16 Gy external boost radiation to the tumour bed or brachytherapy to the tumour bed. Local recurrence rate after breast-conserving surgery varies between 5 and 18%. External boost radiation can partially miss the tumour bed and therefore can result in local failure. Intra-operative radiotherapy (IORT) as a high precision boost can prevent a 'geographical miss'. From October 1998 to December 2000, 156 patients with stage I and stage II breast cancer were operated upon in a dedicated IORT facility. After local excision of the tumour, the tumour bed was temporarily approximated by sutures to bring the tissue in the radiation planning target volume. A single dose of 9 Gy was applied to the 90% reference isodose with energies ranging from 4 to 15 MeV, using round applicator tubes 4–8 cm in diameter. After wound healing, the patients received additional 51–56 Gy EBRT to the whole breast. No acute complications associated with IORT were observed. In 5 patients, a secondary mastectomy had to be performed because of tumour multicentricity in the final pathological report or excessive intraductal component. 2 patients developed rib necroses. In 7 patients, wound healing problems occurred. After a mean follow-up of 18 months, no local recurrences were observed. Cosmesis of the breast was very good and comparable to patients without IORT. Preliminary data suggest that IORT given as a boost after breast-conserving surgery could be a reliable alternative to conventional postoperative fractionated boost radiation by accurate dose delivery and avoiding geographical misses, by enabling smaller treatment volumes and complete skin-sparing and by reducing postoperative radiation time by 7–14 days. © 2002 Published by Elsevier Science Ltd.

Keywords: Breast cancer; Breast-conserving surgery; Intraoperative radiotherapy; Boost radiation

1. Introduction

Surgery, adjuvant hormonal therapy, chemotherapy and radiotherapy are the major elements of modern breast cancer treatment. In 70–80% of breast cancer patients, breast-conserving surgery is possible. In these patients, adjuvant radiotherapy is a well established and accepted therapeutic modality, although controversies about the extent and duration of local radiation therapy exist [1–6].

The standard radiotherapy after breast-conserving surgery consists of 50–55 Gy external beam radiation therapy (EBRT) to the whole breast after 4 weeks of surgery, delivered in fractional doses of 1.7–2 Gy per day for 5–6 weeks followed by an electron boost of 10–16 Gy to the tumour bed.

In a number of patients (5–18%), local recurrence occurs after this treatment. Patients without an electron boost to the tumour bed have a higher local recurrence rate than patients receiving a boost [7–9].

The exact application of the boost is a challenge for the radiotherapist. Reference points for boost application are the scar after surgery and clipping of the tumour bed [10]. A partial geographical miss of the tumour bed could be a reason for local failure [11]. Intra-operative radiotherapy (IORT) by direct application of an electron boost under visualisation of the tumour bed can avoid this geographical miss. A high

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single dose of electrons can be delivered to the tumour bed by keeping normal tissue out of the radiation target volume.

IORT is a well established radiation method for tumours in the abdomen or intrathecal malignancies. The first experiences with IORT in breast cancer were reported in France and in the United States [12–14]. As this kind of radiotherapy is confined to dedicated units and affords close collaboration of surgeons and radiotherapist, it is not yet well established in breast cancer therapy. The advantage of IORT is to deliver one single dose of electrons with varying energies to the tumour bed after excision of the breast cancer while keeping the skin and subcutaneous tissue out of the radiation target volume and thus avoiding or reducing potential fibrous scarring and teleangiectasies with the effect of better cosmesis. IORT reduces the total radiation period for 1–2 weeks and contributes to patient comfort and reduces costs.

2. Patients and methods

Between October 1998 and December 2000, all patients in whom breast-conserving surgery was probable or possible were eligible for this study. 156 patients were included in this prospective study. Four patients had bilateral breast cancer, so a total of 160 intraoperative radiotherapy procedures were performed. Mean age of patients was 57.7 years, ranging from 23.6 to 86.5 years. 8 patients had received neoadjuvant chemotherapy.

In 106/160 procedures (66.3%) a T1 tumour was present, in 53/160 procedures (33.1%) a T2 tumour and in 1 patient a T3 tumour was present. In 99/160 procedures (61.9%), nodal status was negative and in 61/160 procedures (38.1%), the nodal status was positive. Most patients had invasive ductal carcinoma, only a few had invasive lobular or mixed type carcinoma. 32 patients had concomitant ductal carcinoma *in situ*, 3 patients had concomitant lobular carcinoma *in situ*.

In all patients, the diagnosis of breast cancer was obtained preoperatively by core needle biopsy. If patients were eligible for breast-conserving surgery, surgery was planned in the dedicated IORT facility (special unit with linear accelerator in the operating theatre).

In the first step, sentinel lymph node biopsy was performed and was followed by axillary lymph node dissection if the SLN was positive in the frozen section. If the SLN was negative, no axillary lymph node dissection was done. In 71 patients, SLN biopsy without axillary lymph node dissection was performed.

In the second step, the tumour was excised and if the margins were grossly clear by intra-operative pathological evaluation, the tissue surrounding the excision cavity was mobilised and temporarily approximated by sutures, to bring the tumour surrounding tissue in the radiation planning target volume. If the margins were not clear or were closer than 3 mm, re-excision prior to IORT was performed. After this, the tissue depth was measured by intra-operative sonography and by a scaled metallic probe for depth dose prescription. Then the applicator tubes were placed by the surgeon together with the radiotherapist under visual control so that the whole tumour bed and surrounding tissue of approximately 2–4 cm (according to the applicator tube size) were in the radiation target volume. The skin was completely spared from the radiation field. Different applicator tubes with diameters ranging from 4 to 8 cm and lengths from 15 to 25 cm with bevel angles from 0 to 45° were available. After insertion and fixing of the applicator tube, the patient was positioned under the linear accelerator and laser-guided 'air-docked' to the linear accelerator (Philipps Electra SL 18) in our dedicated unit. A single dose of 9 Gy was then applied to the 90% reference isodose with energies ranging from 4 to 15 MeV according to the tissue depth (mean depth 19 mm, range 6–39 mm).

After IORT, the applicator tube and the approximation sutures were removed, the breast was reconstructed and drained and the skin was closed.

After wound healing, patients with invasive ductal carcinoma received an additional 51 Gy/6 weeks (30×1.7 Gy equivalent 52.2–54 Gy ICRU) external beam radiation therapy (EBRT) to the whole breast, patients with invasive lobular carcinoma received an additional 56 Gy (33×1.7 Gy equivalent 57–58.8 Gy ICRU) to the whole breast. The beginning of the EBRT treatment depended on the adjuvant therapy given, for patients with adjuvant hormonal therapy it was started 3–4 weeks after surgery and for patients with postoperative chemotherapy it was started between 4 and 14 weeks, depending on the chemotherapy scheme.

The duration of IORT depended on the applicator tube size and on the tissue depth and electron energies used and lasted only a few minutes. The whole procedure prolonged surgery for approximately 15 to 20 min.

108/156 patients (69.2%) received adjuvant hormonal therapy, 32/156 patients (20.5%) received postoperative chemotherapy, 10/156 patients (6.4%) had combined chemotherapy and hormonal therapy and only 6/156 patients (3.8%) had no adjuvant systemic treatment.

3. Results

3.1. Perioperative complications

In 7 patients (4.4%), early wound healing problems occurred. 2 of these patients developed a haematoma

requiring reoperation. 2 patients developed an abscess and two other patients developed a fistula, 1 patient had a wound healing problem in the axilla.

5 patients had to undergo a secondary mastectomy: 2 because of multicentricity in the final pathological report, 2 patients because of concomitant extensive intraductal carcinoma and 1 patient developed a fistula in the breast after a wound healing problem and underwent a secondary mastectomy and reconstruction with a tram-flap.

In 7 patients, secondary re-excision had to be performed because of close or unclear margins of concomitant intraductal carcinoma in the final pathological report.

3.2. Long-term complications

In 1 patient, abscess incision had to be performed 6 months after the IORT. 2 patients developed rib necroses, 1 required rib resection.

3.3. Local recurrence

After a mean follow-up period of 18 months (minimum 8 months, maximum 35 months), no local recurrences occurred. The cosmetic result was excellent except for the patients with wound healing problems and/or secondary surgery.

4. Discussion

At this time, postoperative EBRT to the whole breast followed by an external boost to the tumour bed by means of brachytherapy or electrons is the postoperative treatment of choice for breast cancer patients in most radiooncological centres. Addition of boost irradiation can significantly reduce the risk of local failure [7–9,15]. Bartelink and colleagues [7] showed, in the European Organization for Research and Treatment of Cancer (EORTC) boost versus non-boost trial, a significant reduction in the local failure rate in the boost group. After a mean follow-up of 5.1 years in 5318 patients given 50 Gy EBRT to the whole breast, this study demonstrated that the addition of a 16 Gy boost could significantly reduce the local failure rate. 182 patients in the non-boost group and 109 patients in the boost group developed local recurrences ($P = 0.0001$). Romestaing and colleagues [9] published similar results after a mean follow-up of 5 years in 1042 patients comparing 50 Gy EBRT plus 10 Gy boost versus non-boost. Local failure rate was 3.6% versus 4.5% in the boost versus non-boost group ($P = 0.044$).

Despite boost radiation, the majority of local recurrences appear in close vicinity to the former primary tumour [16]. A partial geographical miss of the tumour bed could be a reason for this local failure. The target volume for external boost irradiation can be extended, but extension of the boost area leads to a high rate of late reactions in normal tissue such as fibroses and teleangiectases and worsens the cosmetic result.

IORT is a new alternative for boost application in breast cancer patients. The advantage of IORT is the high precision of the boost application directly to the tumour bed and complete sparing of the skin. A geographical miss is unlikely by direct visualisation of the tumour bed and by placing the applicator directly to the target tissue volume. High homogeneity of the dose application and the small treatment volumes are further advantages compared with an external boost application.

In a dedicated unit, surgical procedure is prolonged by IORT for 15–20 min, but the postoperative radiation period is shortened by 7–14 days.

The complication rate appears low, although we experienced two rib necroses. For this reason, we do not use higher single doses than 9–10 Gy IORT. In our unit, all patients received a single dose of 9 Gy IORT to the 90% reference isodose and postoperative EBRT. According to the linear-quadratic model [17,18], we do not believe that higher single IORT doses than 10 Gy are a good choice, as acute and late reactions in normal tissue are severe. Calculation of the biological equivalent dose of a single IORT-dose to fractionated EBRT-dose can be done using the linear-quadratic model (α/β-model). With this model from Barendson and Dale [17], the calculation of the equivalent dose for acute reactions on the tumour and the normal tissue and the late reactions on the normal tissue is possible. According to this model, the application of a single 10 Gy IORT-dose

Table 1
Equivalent dose for acute and late reactions

IORT single dose	Equivalent dose for acute reaction fractionated in 2 Gy ($\alpha/\beta = 10$)	Equivalent dose for late reaction fractionated in 2 Gy ($\alpha/\beta = 3$)
8 Gy	12 Gy (×1.5)	18 Gy (×2.2)
10 Gy	17 Gy (×1.7)	26 Gy (×2.6)
12 Gy	22 Gy (×1.8)	36 Gy (×3.0)
15 Gy	31 Gy (×2.1)	54 Gy (×3.6)

IORT, intra-operative radiotherapy.

corresponds to the biological equivalent of a 17 Gy fractionated dose with respect to the acute reactions on the tumour and the normal tissue, but corresponds to the biological equivalent of a 26 Gy fractionated dose with respect to the late reactions on the normal tissue. That means that a single dose of 10 Gy IORT has a 1.7× isoeffect on the tumour and normal tissue in the acute reaction and a 2.6× isoeffect on the normal tissue in the late reaction compared with fractionated EBRT (Table 1). The application of a higher single IORT-dose leads to an increasing discrepancy between the acute reaction on the tumour and the late reaction on the normal tissue.

Other groups use IORT as a single radiotherapeutic procedure without EBRT. Gatzemeier and colleagues [19] from the Milan group treated 8 patients with 17 Gy IORT, 6 patients with 19 Gy IORT and 33 patients with 21 Gy IORT single dose. These patients did not receive any EBRT. In our opinion, this approach bears the danger of higher local recurrence rates and longer follow-up periods may show side-effects in the normal tissues.

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Further reading

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