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A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated

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Abstract

Local recurrences after breast conserving surgery occur mostly in the quadrant harbouring the primary carcinoma. The main objective of postoperative radiotherapy should be the sterilisation of residual cancer cells in the operative area, while irradiation of the whole breast may be avoided. We have developed a new technique of intra-operative radiotherapy (IORT) of a breast quadrant after the removal of the primary carcinoma. A mobile linear accelerator (linac) with a robotic arm is utilised delivering electron beams able to produce energies from 3 to 9 MeV. Through a perspex applicator, the radiation is delivered directly to the mammary gland and to spare the skin from the radiation, the skin margins are stretched out of the radiation field. To protect the thoracic wall, an aluminium-lead disc is placed between the gland and the pectoralis muscle. Different dose levels were tested from 10 to 21 Gy without important side-effects. We estimated that a single fraction of 21 Gy is equivalent to 60 Gy delivered in 30 fractions at 2 Gy/fraction. Seventeen patients received a dose of IORT of 10 to 15 Gy as an anticipated boost to external radiotherapy, while 86 patients received a dose of 17–19–21 Gy intra-operatively as their whole treatment. The follow-up time of the 101 patients varied from 1 to 17 months (mean follow-up time was 8 months). The IORT treatment was very well accepted by all of our patients, either due to the rapidity of the radiation course in cases where IORT was given as the whole treatment or to the shortening of the subsequent external radiotherapy in cases where IORT was given as an anticipated boost. We believe that single dose IORT after breast resection for small mammary carcinomas may be an excellent alternative to the traditional postoperative radiotherapy. However, a longer follow-up is needed for a better evaluation of the possible late side-effects. © 2001 Published by Elsevier Science Ltd. All rights reserved.

Keywords: IORT, Breast; BCS; Post-operative radiotherapy

1. Introduction

Intra-operative radiotherapy (IORT) is a radiotherapeutical technique which delivers a single dose of radiation directly to the tumour bed or to the exposed tumour during surgery, with curative or palliative intent. It is mainly used as an adjuvant to surgery or as an anticipated boost to be followed by fractionated external beam radiotherapy. The objective is to achieve higher doses to the target volume, while surgically displacing dose-limiting structures. There are only few reports on small series of patients treated with IORT in early breast cancer [1–3], and all the reports consider IORT as an 'intraoperative boost' to a course of conventional postoperative external radiotherapy. This approach has been demonstrated to prevent local recurrences in selected stage I and II breast cancer cases, while no significant complications were associated with IORT, and patients always enjoyed excellent cosmetic results.

The results of a Milan randomised trial on the role of postoperative radiotherapy after breast conserving surgery [4] after 12 years of follow-up have shown that 85% of local relapses occur in the operative area. The remaining 15% of cases, occurring in different quadrants should be considered new ipsilateral carcinomas.

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As the majority of local recurrences after conservative surgery for breast carcinoma are expected in the same anatomical area of surgery, the main objective of radiotherapy should be directed to the destruction of residual cancer cells in the operative area. The irradiation of the whole mammary gland may have only one role that is to prevent new ipsilateral carcinomas and, to be consistent, should be delivered to both breasts. A previous trial on limited field radiotherapy after breast conservation published in 1993 [5] showed a limited increased rate of local recurrences, mainly for lobular invasive carcinomas, but no difference in survival.

At the European Institute of Oncology in Milan, we recently performed a dose-escalation study for IORT treatment of breast carcinomas with a diameter less or equal than 2.5 cm, to test the feasibility of IORT as the whole radiotherapy treatment and not only as a boost in the conservative approach to breast carcinoma.

2. Patients and methods

From July 1999 to September 2000, we performed 103 IORT treatments in 101 consecutive patients (2 patients received bilateral IORT) affected by infiltrating carcinoma of the breast with a mammographic or ecographic diameter equal or inferior to 2.5 cm who agreed to have the intra-operative treatment. The mean age of the patients was 58 years (range 33–80 years). We excluded from the study patients with medical contraindications to radiation therapy and patients with a tumour located in the axillary tail of the breast. Patients with *in situ* carcinoma or with invasive carcinoma with extensive intraductal component were also considered not to be eligible. An informed consent was signed by the patient.

43 patients underwent breast resection and axillary dissection, 53 underwent breast resection and sentinel node biopsy, 5 patients received simple resection of the breast. The characteristics of the patients are shown in Table 1.

We tested different radiation dose-levels: 10, 15, 17, 19 and 21 Gy (Table 2). The dose of electrons was prescribed at the depth of maximum dose (D_{max}) for the first 55 patients [6]. 46 additional patients received the planned dose (21 Gy) at the level of the 90% isodose, since we observed, analysing the preliminary results, that approximately 20% of the patients with a residual breast thickness of 25 mm or more received an underdosage at the deepest part of the target volume. This modification brought the maximum dose to 23.3 Gy and improved the coverage of the target volume, with only 5% of the patients receiving slightly less than 80% of the prescribed dose on a very limited area of the breast target volume.

We reached the 21 Gy dose-level without major acute side-effects. Based on the radiobiological models used to predict radiation effects (Linear-Quadratic Surviving Fraction or Multitarget Surviving Fraction) [7], we can estimate that a dose of 60 Gy delivered in 30 fractions at 2 Gy/fraction, which is the radiation dose required to control microscopical residual disease after breast resection, is equivalent to a single fraction of 20–22 Gy, when using an α/β ratio at 10 Gy, typical for tumours and acute reacting tissues. Using the same equation, but calculating the tolerance of late responding tissues (α/β ratio at 3 Gy) this equivalent value rises to at least 110 Gy. Patients in the two initial dose levels (10 and 15 Gy) received further conventional fractionated radiotherapy (44 and 40 Gy, respectively).

Table 1
Main characteristics of the patients

	No. of cases (101)	%
Tumour size (mm)		
⩽5	2	2
6–10	21	21
11–15	38	37
16–20	23	23
>20	17	17
Tumour site (quadrant)		
Upper outer	50	49
Upper inner	5	5
Lower inner	13	13
Lower outer	16	16
Central	3	3
Superior (middle nipple line)	11	11
External (equatorial)	3	3
Histology		
Invasive ductal carcinoma	74	73
Invasive lobular carcinoma	9	9
DCIS	3	3
Other	15	15
Tumour grade		
G1	26	26
G2	41	40
G3	34	34
Hormonal receptor status		
Oestrogen+	85	84
Oestrogen−	16	16
PgR+	72	71
PgR−	29	29
Proliferative rate (Ki67)		
⩽20%	58	57
>20	43	43

PgR, progesterone receptor; DCIS, ductal carcinoma *in situ*.

Table 2
IORT dose levels

Dose level (Gy)	Aim	No. of patients (*n*)
10	Anticipated boost	10
15	Anticipated boost	7 (1 bilateral)
17	Whole treatment	8 (1 bilateral)
19	Whole treatment	6
21	Whole treatment	70 (46 patients at 90% isodose)

IORT, intraoperative radiotherapy.

2.1. Radiation treatment device

Novac7 (Hitesys SpA, Italy) is a mobile dedicated linear accelerator (linac) for IORT, whose radiating head can be moved by an articulated arm and which can work in an existing operating room (Fig. 1). This linac does not produce photons, but only delivers electron beams at four different nominal energies: 3, 5, 7, 9 MeV, corresponding to 4.5, 5.2, 6.5, 7.8 MeV most probable energies at the phantom surface, respectively. Radiation beams are collimated by means of a hard-docking system, consisting of 5 mm thick perspex round applicators. Both flat-ended and angled (22.5° and 45°) applicators and different diameters (4, 5, 6, 8, 10 cm) are available. The nominal source to surface distance (SSD) is 100 cm for a 10 cm tube and 80 cm for the other ones. For each energy, depth dose curves strongly depended on the bevel angle, while no significant dependence on applicator size was noted. The depth of the 80% isodose ranged between 13 mm (3 MeV) and 24 mm (9 MeV). At the 9 MeV energy level, for the 22.5° and 45° angled applicator such depth was seen to decrease to 21 and 17 mm, respectively. The depth dose curves for a 10 cm-diameter flat applicator are shown in Fig. 2.

For radiation protection reasons, a primary beam stopper, consisting of a lead shield 15 cm thick, mounted on a trolley and three mobile barriers (100 cm length, 150 cm height and 1.5 cm lead thickness) are provided.

Electron beams are delivered by Novac7 with very high dose/pulse values, compared with those supplied by conventional medical linacs. Hence, the uncertainty in the determination of the ion recombination factor makes the use of parallel-plate ionisation chambers not reliable for beam dosimetry. Radiochromic films (MD-55-2, lot no. 38055, International Specialty Products, Inc.), in forms of 1.5×1.5 cm^2 individual dosimeters, and mailed chemical Fricke dosimeters (prepared and analysed by ENEA, Centro Ricerche Casaccia, Rome, Italy) were used for beam calibration. Routine output constancy measurements were carried out using a flat ionisation chamber (Markus type, PTW) in a water-equivalent phantom.

Environmental dosimetry was performed using a radiation monitor (RPO-50, Victoreen), with the beam stopper and the three mobile shielding barriers positioned inside the operating room to simulate the clinical conditions.

2.2. Surgery

The breast resection is performed either by radial or circular incision with safety margins of 1 cm or more around the tumour. A frozen section assessment for histology, focality, dimensions and extent of resection margins is performed at the time of surgery and before the IORT procedure. The definitive finding of the surgical

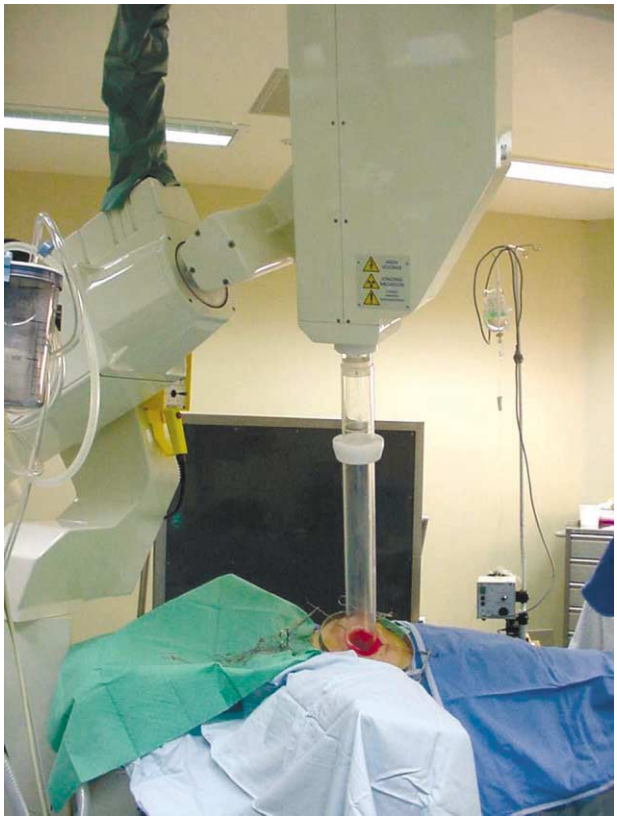

Fig. 1. The dedicated Novac 7 linear accelerator placed in the operating room during a dosimetry procedure. The primary beam stopper and one of the mobile shielding barriers are also shown.

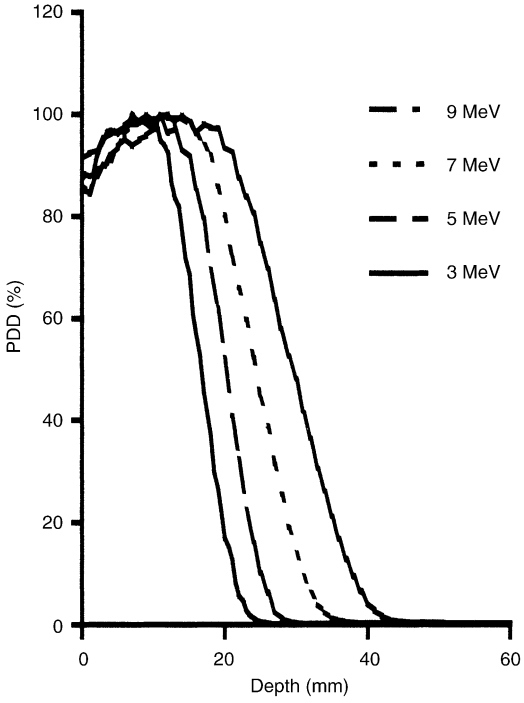

Fig. 2. Percent depth dose curves (PDD) measured in a water phantom for a flat applicator (10 cm diameter).

specimen is obtained 2 or 3 days later. An X-ray film of clinically non-palpable lesions is performed after their surgical removal, in order to verify the presence of the lesion, its centricity and the extent of the resection margins. Unless otherwise indicated, sentinel node biopsy is performed.

Once the breast resection has been performed, the deep face of the breast is separated from the pectoral muscle for 5–10 cm around the tumour bed, and the superficial margins are also carefully separated from the skin for 3–5 cm in every direction.

In order to minimise the irradiation of the thoracic wall and to guarantee the delivery of the full radiation dose to the breast itself, dedicated aluminum–lead disks (4 mm Al + 5 mm Pb thick) of various diameters (from 4 to 10 cm) are placed between the deep face of the residual breast and the pectoralis muscle (Fig. 3). Immediately after the mobilisation of the breast and the placement of the protection of the disks, we suture the mammary gland in the area of the breach left by the removal of the tumour. The result is the restoration of the anatomy of the residual breast, taking into account the need to maintain its thickness as homogeneously as possible, in order to allow a good dose distribution in the target volume. The thickness of the target volume is measured by a needle and a ruler in at least three points of the breast portion to be irradiated, and taking into consideration the average value.

To completely spare the skin from the radiation dose, the skin margins are stretched out of the radiation field using a home-made device consisting of a metallic ring furnished with four hooks (Fig. 4). We also put a wet sterile gauze between the skin and the applicator's edge to introduce a further tissue-equivalent barrier, able to absorb the low energy electrons scattered around by the applicator itself.

2.3. Radiation treatment delivery

The clinical target volume (CTV) consists of the residual breast after the resection, limited to the anatomical area corresponding to the previously involved quadrant. The margins of the planned target volume encompass the entire circumference of the tumour bed (1–3 cm around the sutured surgical breech, according to the tumour diameter and the breast volume). The base of the excision site is also considered as part of the target. A proper applicator's diameter is then selected and visually placed directly in contact to the breast. The remote control of the linac allows the safe docking procedure. The optimal energy of the electron beam is selected on the basis of the previously measured target thickness. The primary beam stopper and the three mobile barriers are positioned, below and around the operating table, in order to provide a good shielding of the stray radiation and all the personnel leave the operating room. Immediately after, acting on the control panel (external to the operating room), the irradiation is performed in two consecutive steps. In the first step, half of the expected linac monitor units are delivered and than the number of radiation pulses actually given is recorded. In the second step, the remaining number of the monitor units is eventually compensated in order to globally ensure the delivery of the planned number of pulses. In other words, this two-step procedure allows a control of the pulses really delivered. The choice of this procedure is due to the fact that output constancy measurements showed a significant dependence (up to 10%) of the response of Novac7 unsealed monitor chambers on environmental humidity. For that reason, dose/pulse, appearing quite stable, was considered as a reference parameter also for beam calibration, instead of the more familiar dose/monitor unit. In our clinical practice,

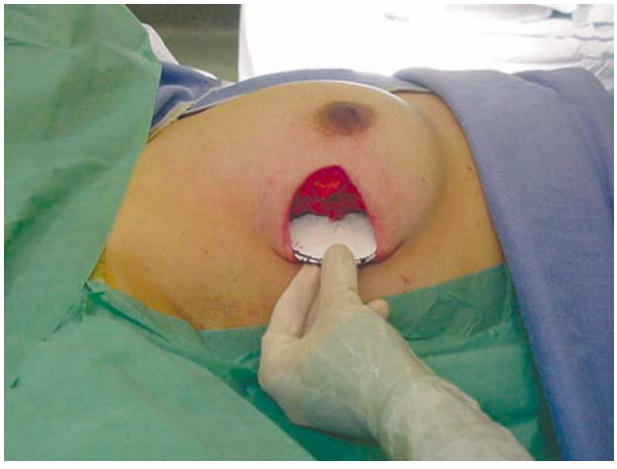

Fig. 3. Before the intraoperative radiotherapy (IORT) treatment delivery, an aluminium-lead disk (4 mm Al + 5 mm Pb thick) of proper diameter is placed between the deep face of the residual breast and the pectoralis muscle. This allows the irradiation of the thoracic wall to be minimised.

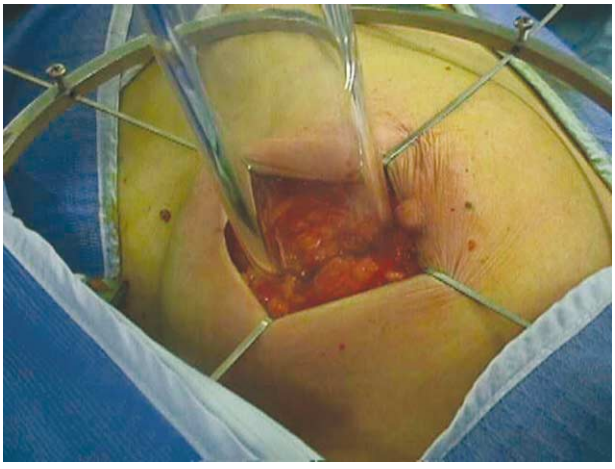

Fig. 4. Close-up view of the proper placement of the applicator in the breast. To completely spare the skin from the radiation dose, the skin margins are stretched out of the radiation field using a home-made device consisting of a metallic ring furnished with four hooks.

the difference between the 'planned' radiation pulses and the 'actually delivered pulses' was never greater than $\pm 1.5\%$.

The whole procedure of irradiation is completed in less than 2 min. After the delivery of the radiation treatment, the applicator and the aluminum-lead disk used for the protection of the thoracic wall are removed and the surgeons can complete the definitive breast reconstruction.

At the beginning of our IORT experience, we decided to give patients an antibiotic prophylactic therapy during the induction of anaesthesia (not routinely offered to patients who receive breast-conserving surgery) as a precaution against the risk of postoperative infection, prolonging it until the fifth day after surgery.

3. Results

10 patients received a IORT dose of 10 Gy as an anticipated boost followed by conventional fractionated external beam irradiation at the total dose of 44Gy/22 fractions. Seven patients received 15 Gy of IORT followed by external beam irradiation at a total dose of 40 Gy/20 fractions. The other 84 patients received a dose of 17–19–21 Gy intraoperatively as their sole treatment. The follow-up time of the 101 patients varied from 1 to 17 months (mean follow-up time was 8 months). 10 patients experienced mild/intermediate acute toxicity: 2 of them (both treated with 21 Gy IORT) suffered postoperative infections. Other side-effects included mild pain (grade 2) in the irradiated area (2 patients), local haematoma (3 patients) and transitory oedema (grade 1 or 2) of the breast tissue (3 patients). Late toxicity has been evaluated according to the Lent Soma scales for breast, even though the short follow-up time does not allow a full assessment of this aspect. Only 1 patient who received a 10 Gy IORT as a boost followed by a course of external fractionated radiotherapy suffered a severe fibrosis (grade 3) from irradiation. 5 additional patients (5%) suffered fibrosis of the treated area of grade 1 or 2. Of these 5 patients, 1 received 15 Gy IORT and underwent external radiotherapy after surgery to complete the radiation course, while the others received 21 Gy IORT as their definitive treatment.

From the oncological point of view, 1 patient developed bone metastases three months after surgery: this patient had received 15 Gy IORT as an anticipated boost.

The IORT treatment was very well accepted by all patients, either due to the rapidity of the radiation course in the case of IORT as a whole treatment or to the shortening of the subsequent external radiotherapy in cases of IORT as an anticipated boost. Moreover, patients treated with IORT did not suffer immediate skin erythema because of the complete avoidance of the skin during the irradiation.

In 1 year of activity, the mean time needed to perform all the phases of IORT decreased from 40 to 20 min, due to the improved experience of the team.

In cases where sentinel node biopsy was performed, the time spent for IORT covered the time needed for the intra-operative histological examination of the sentinel node, thus there was no prolongation of the surgical time.

Personnel involved in IORT rapidly developed a good expertise and the integration between the Radiotherapy Division and the Breast Surgery Division allowed a good selection, treatment and follow-up of the patients.

4. Discussion

In order to avoid a prolonged course of external irradiation, several authors have treated patients with low or high dose-rate iridium implants to the primary tumour bed alone as part of the breast conserving protocol [8,9]. The local control rate was very high (from 92 to 100%) in all of the trials except one [10]. It is worthwhile to mention that in all of the trials reported above, the cosmetic result was comparable to that of conventional approach and the incidence of distant metastases and overall survival was similar to those treated with a combined radiation treatment.

External beam breast irradiation directed to the tumour bearing quadrant alone has also been compared with whole breast irradiation in clinical node-negative patients with a tumour diameter less than 4 cm [5]. This randomised trial compared two different techniques which followed tumour excision: one irradiating the whole breast and the regional lymph nodes, the other with an electron field confined to the tumour bed alone. There was a clear advantage in local control for whole breast irradiation: at 8 years of median follow-up, the crude breast recurrence rate was 19.5% in the limited irradiation group and 10% in those who received whole breast irradiation. When considering the recurrence rate in the breast as the sole modality of failure, the difference was smaller: 6% versus 4%. In addition, in this study there was an unbalanced prevalence of lobular carcinoma in the arm treated with the limited field, the schedule of radiation therapy was very unusual and none of the patients received systemic therapy [5,11].

The experience on 101 patients treated with IORT (84 as a whole treatment) allows a positive preliminary conclusion. The procedure is simple and rapid, the training of the staff easy, the acute side-effects are minimal and not serious. The patients' satisfaction is high, as the long period for the external radiotherapy is avoided.

IORT dramatically reduces radiation exposure of the skin, of the lung, and of the subcutaneous tissues and completely avoids the irradiation of the controlateral breast, contributing to a very low incidence of radiation-induced sequelae.

IORT for limited-stage breast carcinoma only briefly prolongs the duration of the surgical procedure. In cases where the sentinel node is biopsied, the time spent for IORT covers the time needed for the intraoperative histological examination of the sentinel node, thus there is no prolongation of the surgical time.

However, a longer follow-up is needed for a careful evaluation of the possible late effects of IORT.

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