Intraoperative Radiation Therapy for Breast Cancer: Technical Notes

Umberto Veronesi, MD,* Giovanna Gatti, MD,* Alberto Luini, MD,* Mattia Intra, MD,* Roberto Orecchia, MD,† Patrick Borgen, MD,‡ Michael Zelefsky, MD,§ Beryl McCormick, MD,§ and Virgilio Sacchini, MD‡

**Breast and †Radiation Oncology Departments, European Institute of Oncology, Milan, Italy, and ‡Breast Service, Department of Surgery, and §Radiation Oncology Department, Memorial Sloan-Kettering Cancer Center, New York, New York*

■ **Abstract:** Interest in intraoperative radiation therapy (IORT) for breast cancer is increasing as the possible benefits of this technique for the patient become apparent. The rationale for the use of this segmental radiation therapy in place of whole-breast irradiation is based on the finding that approximately 85% of breast relapses are confined to the same quadrant of the breast as the primary tumor. Phase I and II trials have demonstrated no increase in postsurgical complication rates following the use of single-dose IORT in localized breast cancers. Longer follow-up is needed to assess the cosmetic outcome. Clinical trials to evaluate the effectiveness of IORT in the treatment of breast cancer are currently under way at the European Institute of Oncology (EIO) at the University of Milan, Italy, and at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. Here we report the two different techniques in use in these trials. ■

Key Words: breast cancer, intraoperative radiation therapy, surgical technique

Interest in intraoperative radiation therapy (IORT) for breast cancer is increasing as the possible benefits of this technique for the patient become apparent. The ability to deliver a single therapeutic dose of radiation to the tumor bed during surgery, and thereby avoid the standard 6-week course of external-beam treatment, may benefit patients by alleviating the psychological distress caused by the need for a relatively protracted course of treatment, reducing the associated financial burden for both the patient and health care system, and allowing earlier return to normal life.

The rationale for the use of this segmental radiation therapy in place of whole-breast irradiation is based on the finding that approximately 85% of breast relapses are confined to the same quadrant of the breast as the primary tumor (1). Tumoral foci are usually located in close proximity to the primary tumor, and residual microscopic disease occurring in the same quadrant as the resection is often the cause of local disease recurrence. Phase I and II trials have demonstrated no increase in postsurgical complication rates following the use of single-dose IORT in localized breast cancers. Longer follow-up is needed to assess the cosmetic outcome, which may be impaired by fibrotic changes in the breast tissue secondary to irradiation with this high dose of radiation without fractionation. Clinical trials are currently under way at the European Institute of Oncology (EIO) at the University of Milan, Italy, and at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY, to investigate the safety of single-dose IORT from the oncologic point of view, and to compare the rate of local control achieved

Address correspondence and reprint requests to: Virgilio Sacchini, MD, Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., MRI-1026, New York, NY 10021, USA, or email: sacchinv@mskcc.org.

with this procedure with that seen in conventional external-beam treatment. Here we report the two different techniques in use in these trials to evaluate the effectiveness of IORT in the treatment of breast cancer.

THE LINEAR ACCELERATOR ELECTRON BEAM ADMINISTRATION TECHNIQUE

This method has been used at the EIO in a pilot phase I trial in which different radiation dose levels were administered to reach a 21 Gy dose level prescribed at the 90% isodose curve (2). Based on the radiobiologic models used to predict radiation effects (linear-quadratic surviving fraction or multitarget surviving fraction), it was estimated that a single fraction of 20–22 Gy is equivalent to a dose of 60 Gy delivered in 30 fractions of 2 Gy each, the conventional dose used to treat patients following breast-conserving surgery.

The EIO trial used the Novac7 (Hitesys S.p.A., Aprilia [LT], Italy), an accelerator that has a robotic arm and weighs approximately 1100 lb and measures 232 cm in length, 114 cm in width, and 199 cm in height. This device can be moved easily into an operating room and can deliver electron beams at four different normal energies: 3, 5, 7, and 9 MeV. Radiation beams are collimated by means of a 5 mm-thick Perspex tube, known as the "hard docking," composed of two parts, one which is sterile and managed by the surgeon, and the other which is managed by the radiation oncologist. The two parts are connected once the first has been placed in the operative field. This ensures maximum precision in alignment, thus providing very high-dose reproducibility. The lower portion of this tube, located at the operatory bed, may be 4, 5, 6, 8, or 10 cm in diameter, according to the size of the irradiation field.

The accelerator's floor-stand structure, its articulated arm with four rotational joints, and its motorized base allow translator movements of the entire structure without modifying head orientation. The electron beams are delivered perpendicular to the tissue, with the depth of the 80% isodose ranging from 13 (3 MeV) to 24 mm (9 MeV). At the 9 MeV energy level, for the 22.5-degree and 45-degree angled applicators, the depth was decreased to 21 and 17 mm, respectively.

The surgical excision of the tumor in the Milan IORT trial was done in the standard way: quadrantectomy with 1–2 cm grossly free margins, usually including a small ellipse of skin. The excision extends to the fascia of the pectoralis major muscle, which is usually removed with the specimen. Particular attention is paid to the surgical margins. Effort should be made to decrease the risk of positive surgical margins on final pathology, so as to avoid the need for a potentially problematic reexcision. This quadrantectomy procedure is in no way different from that normally performed outside of the clinical trial setting.

The use of IORT administration alters subsequent surgical technique. Following quadrantectomy, the breast tissue is usually reapproximated in order to close the breast surgical wound. When IORT is performed, which is delivered by a vertical-perpendicular beam to the tissue, the breast tissue must be detached from the underlying skin and the skin retracted to avoid skin necrosis secondary to high-dose irradiation. An aluminum-lead disk is then positioned on the surface of the pectoralis major muscle as a safety precaution, to prevent any irradiation of the chest wall (Fig. 1A). Placement of this disk requires that the residual breast tissue be disconnected from the pectoralis major fascia for 3–4 cm. The two breast tissue flaps, anteriorly disconnected from the skin and posteriorly disconnected from the muscular fascia, are temporarily stitched together above the metal disk (Fig. 1B). The thickness of the breast tissue flaps is measured with a needle and ruler at a minimum of three points on the portion of the breast to be irradiated, and the average thickness is taken into consideration when determining the radiation dose.

The irradiation tube is inserted past the retracted skin, directly to the breast tissue (Fig. 2A). Wet gauze is placed between the skin and the applicators edge (Fig. 2B). The area of the flaps lying above the metal disk and directly beneath the cathodic tube is then irradiated. The entire irradiation procedure is completed in 2 minutes The dose/pulse calculation has been previously described at length (2). Figure 3 shows the isodose curves of the linear accelerator electron beam administration by angulation of the cathodic tube.

THE HIGH DOSE RATE REMOTE AFTERLOADING IORT TECHNIQUE

This method is currently in use in a pilot clinical trial at MSKCC. The IORT in this trial is administered by means of a high dose rate remote afterloading system that uses an iridium 192 (Ir192) source to deliver high dose rate brachytherapy to the tumor bed. The catheters for the iridium source are contained in a quadrangular silastic template, available in different sizes and with a varying number of catheters according to the volume to be irradiated. This template is inserted in the cavity with the deep margin resting on the pectoralis major muscle. From a surgical point of view, the main difference between this

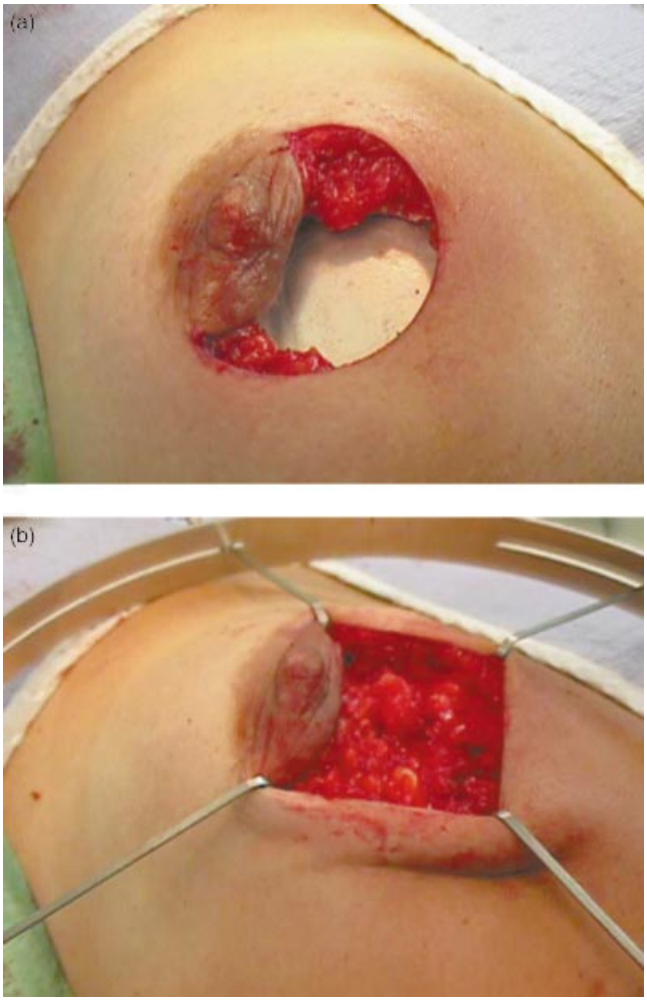

Figure 1. Linear accelerator electron beam administration. (A) Following quadrantectomy, an aluminum-lead disk is positioned on the surface of the pectoralis major muscle as a safety precaution to prevent any irradiation of the chest wall. (B) The two breast tissue flaps are temporarily stitched together above the metal disk. The skin is pulled away from the field.

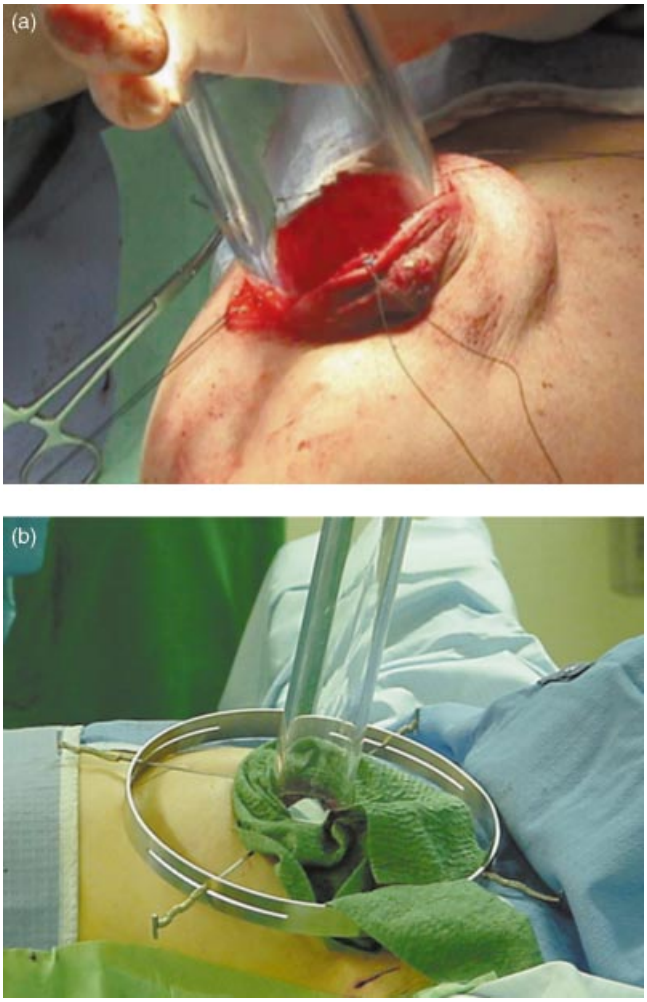

Figure 2. (A) The cathodic tube is inserted and the flaps lying above the metal disk are then irradiated. (B) Wet gauze is placed between the skin and the applicator's edge.

technique and the one described previously is that with this high dose rate remote afterloading technique, it is not necessary to widely detach the breast tissue from the skin or from the underlying fasua of the pectoralis major muscle following wide local excision and an aluminum-lead disk is not placed over the pectoralis major. Radiation distribution occurs along the catheters, diffusing transversely in the breast parenchyma; therefore, the skin and the pectoral surface receive minimal radiation. We also remove only a small ellipse of skin, especially when the tumor is superficial, and the fascia of the pectoralis major muscle is included as the deep margin of the specimen (Fig. 4A). Delivery of the radiation transversely is not expected to significantly increase the risk of positive posterior and

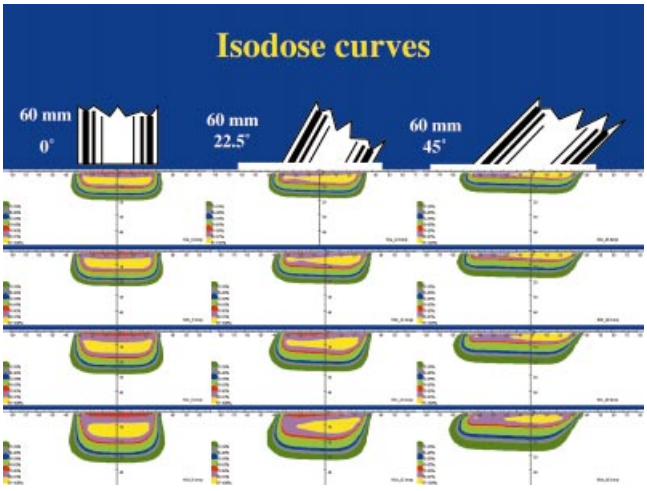

Figure 3. Isodose curves of the linear accelerator electron beam administration by angulation of the cathodic tube.

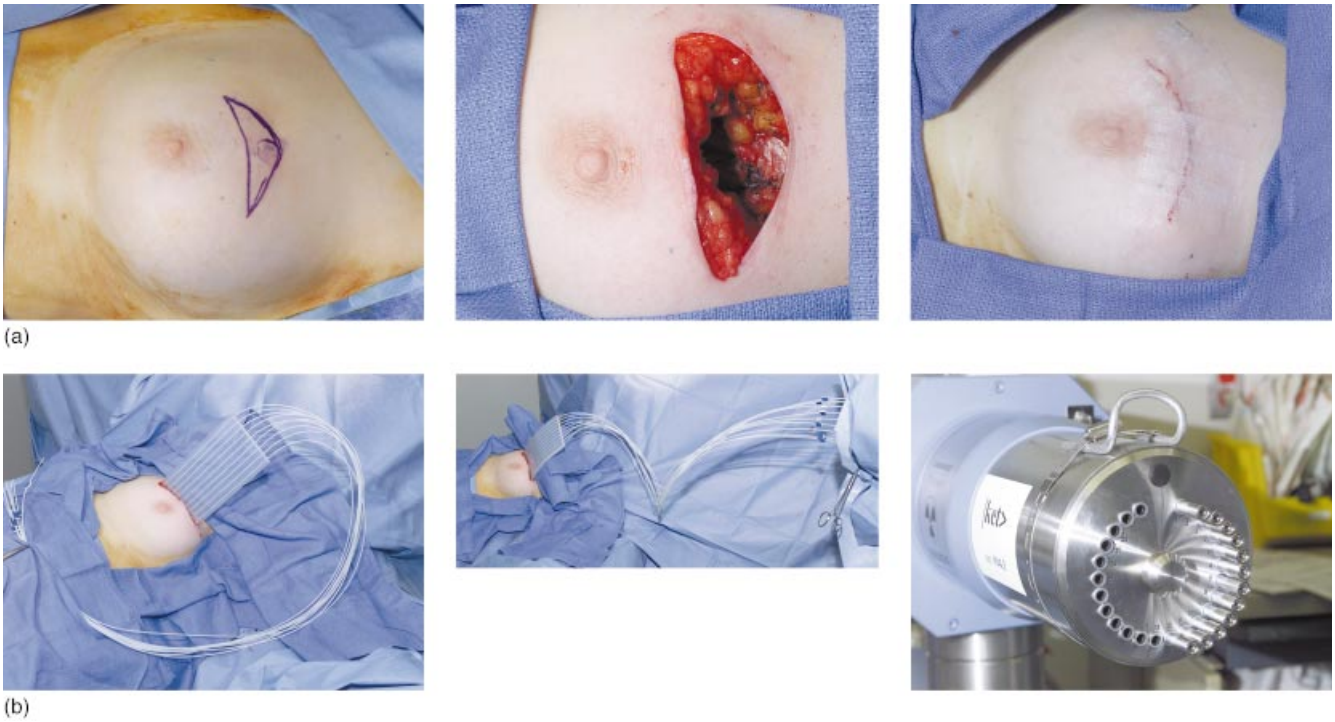

Figure 4. High dose rate remote afterloading IORT. (A) Wide excision with removal of the fascia of the pectoralis major muscle. (The third photograph in this sequence shows the closed incision, following completion of the quadrantectomy and IORT procedures.) (B) The H.A.M. applicator is inserted into the cavity with the deep margin resting on the pectoralis major muscle. Once the applicator is in position in the lumpectomy cavity, catheters are connected in the appropriate sequence.

anterior resection margins, nor is it expected to affect cosmesis.

In an attempt to reduce as much as possible the risk of an involved margin (clear margins are also a criterion of initial case selection), we implemented the following procedure. The specimen, once removed, is labeled with two stitches, one short superior and one long lateral. In addition, one radiopaque clip is secured to the short wire (superior margin) and two to the long wire (lateral margin). The specimen is then placed carefully on a Plexiglas plate, with the deep margin down. A radiograph of the specimen is then obtained. This radiograph is useful in identifying the concentricity of the lesion in the specimen. An additional margin is usually removed if the lesion appears to be too close to the margin.

The specimen is then sent to pathology, where it is grossly analyzed. Particular attention is paid to any close margins. In the case of a close margin, the surgeon is advised to perform an immediate additional resection of that margin. If a diagnosis of malignancy is made on cytology only, a histologic confirmation is required either by performing a core/open biopsy or frozen-section analysis.

The breast parenchyma must be as flush with the H.A.M. silastic applicator (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY) as possible. To achieve this, it may be secured by two to three stitches done with a 1-0 curved needle running through the breast parenchyma and the silastic applicator. Once the applicator has been carefully positioned and secured in the lumpectomy cavity, catheters are connected (Fig. 4B). These tubes are then connected to the afterloader in the appropriate sequence.

While the H.A.M. applicator is being placed, computer-based dosimetry is generated to calculate and optimize the isotope dwell times required to achieve optimal dose distribution within the cavity. The computer program has the ability to modulate the homogeneity of the radiation as required and specifically define points within the target region that require intensification or diminution of the dose (Fig. 5). The radiation dose is prescribed at 1 cm from the surface of the applicator, and in general the prescribed dose is 20 Gy. The computer plan is generated in 5 minutes and evaluated by the radiation oncologist. The computer-optimized dwell times (length of time for which the radiation source is positioned at various locations along the catheters within the breast cavity or target volume) are input into the treatment computer operating the afterloading machine. This machine controls the

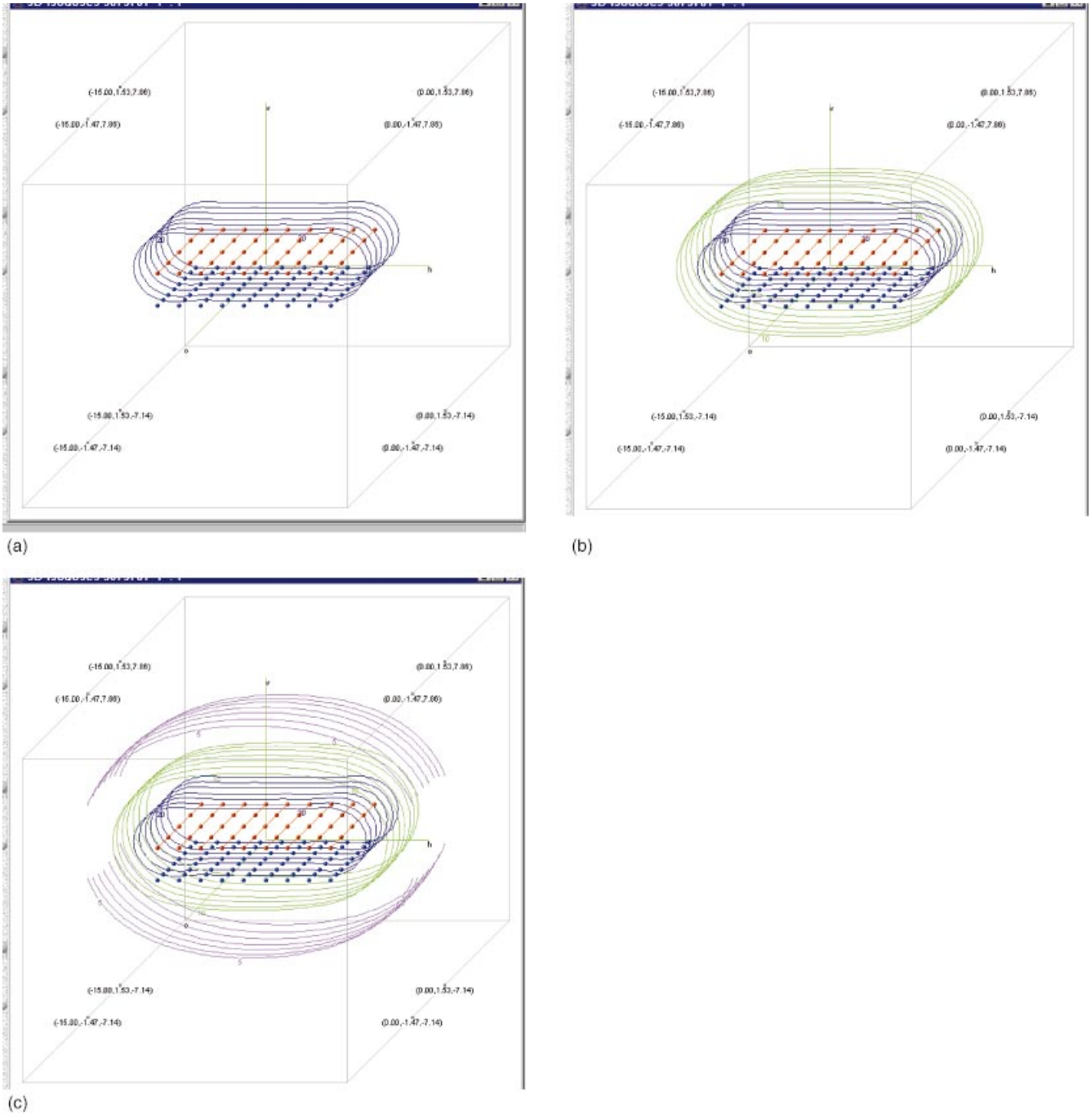

Figure 5. Isodose curves of the high dose rate remote afterloading

delivery of the source at the predetermined position in the applicator at the prescribed dose.

For safety reasons, personnel must leave the room for the entire irradiation period. A special anesthesiology monitoring station is available outside the room. The electrocardiogram (EKG) and all ventilatory parameters are reported on an outside collimated monitor and special cameras in the operating room are focused on the patient, IV device, and operatory field. When local anesthesia with sedation has been used, the anesthesiologist should check that the patient is properly sedated in order to avoid gross movement by the patient. Following completion of IORT procedure, the H.A.M. applicator is removed, the breast parenchyma is reapproximated, and the breast cavity is closed.

The calculated cost of treatment using the high dose rate remote afterloading IORT technique is significantly less than of 6-week external-beam radiation treatment.

DISCUSSION

The concept of segmental radiation therapy of the breast was developed following the observation that approximately 85% of local relapses after conservative surgery and radiation therapy for breast cancer occur in the same anatomic quadrant of the breast as the primary tumor. This is coherent with the pathology observation that breast cancer is a multifocal rather than multicentric phenomenon. In two studies (3,4) that looked at the distribution of cancer within the breast, researchers performed exhaustive sectioning of breast specimens with topographic correlation and noted that the foci around the main tumor are confined to the same quadrant in more than 90% of cases.

So-called second primary ipsilateral tumors occur in a minority of cases and have a frequency comparable to that of contralateral breast cancer. This observation led to both the RTOG Cooperative Group Phase II brachytherapy trial (5) and to a similar study at the William Beaumont Hospital (6,7). These studies delivered quadrant radiation to the breast over a period of 1 week or less using a technique of implanting catheters loaded with radioactive sources. Patients were carefully selected based on a diagnosis of unifocal, stage I or II invasive ductal carcinoma. Early reports of these studies demonstrated excellent local control.

Some of the selection criteria for these two trials have been applied in the clinical studies in progress at the EIO in Milan and MSKCC in New York. The first criterion was age. A recent "intergroup" phase III trial comparing tamoxifen alone with tamoxifen plus a standard 6-week course of external-beam breast radiation in women ≥70 years of age with stage I, estrogen-positive breast cancer showed no difference in survival or disease-free survival between the two groups. With a median follow-up of 28 months, 4 of 317 women in the tamoxifen group and none of the women in the radiation group developed a breast local failure (8). This finding confirmed prior observations by Veronesi et al. (9), that the local failure rate after standard breast-conserving surgery and radiation is much lower in older women (more than 55 years of age), and introduced the hypothesis that less than "standard" radiation may provide equivalent local control in older women.

The second important criterion is unifocality of the tumor on physical and instrumental examination (mammography with or without ultrasound). An extensive intraductal component on the previous core or open biopsy is also considered an exclusion criterion, due to the associated higher risk of local recurrence. The Milan Institute has entered the third phase of their investigation of IORT for breast cancer, randomizing women ≥48 years of age to receive either conventional external-beam radiation therapy or IORT. This is a clinical trial based on equivalence. Its aim is to demonstrate that the incidence of local recurrences at 5 years in the quadrantectomy plus IORT arm of the study is not statistically different from that seen in the external-beam radiation arm. The calculated sample size is 412 patients per arm, for a total sample size of 824 patients. MSKCC has entered the second phase of its investigation with the alternate method and intends to recruit 50 women before starting the randomized clinical phase (phase III).

One questionable point of IORT treatment is the delivery of high-dose radiation therapy in a single fraction. The major concern is possible necrosis of the tissue with increased postoperative complications or late fibrosis affecting cosmesis. The EIO experience seems reassuring on this point, but longer follow-up is necessary for satisfactory cosmetic assessment.

As emphasized in a commentary on our previous article (10), the results of long-term follow-up of planned phase III trials must be obtained before IORT can be applied in routine clinical practice. The present article is an explanation of the methods of IORT currently in use, including the problems associated with each, and is intended to inform the surgical and radiologic communities of this new approach and, where possible, facilitate participation in clinical studies.

REFERENCES

1. Veronesi U, Marubini E, Mariani L, *et al.* Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 2001;12:997–1003.

2. Veronesi U, Orecchia R, Luini A, *et al.* A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 2001;37:2178–83.

3. Gump FE, Shikora S, Habif DV, *et al.* The extent and distribution of cancer in breasts with palpable primary tumors. *Ann Surg* 1986;204:384–90.

4. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56:979–90.

5. Hanson W, Martin E, Kuske RR, *et al.* Dose specification and quality assurance of RTOG protocol 95-17: a cooperative group study of 192Ir breast implants as sole therapy. www.rtog.org/protocols.html.

6. Vicini FA, Chen PY, Fraile M, *et al.* Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys* 1997;38:301–10.

7. Baglan KL, Martinez AA, Frazier RC, *et al.* The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 2001;50:1003–11.

8. Hughes K, Schnaper L, Berry D, *et al.* Comparison of lumpectomy plus tamoxifen with and without radiotherapy in women 70 years of age or older who have clinical stage I estrogen receptor positive (ER+) breast cancer. *Proc Am Soc Clin Oncol* 2001;20:24A.

9. Veronesi U, Luini A, Del Vecchio M, *et al.* Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993;328:1587–91.

10. Bartelink H. Commentary on the paper "A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated." A critical review of an innovative approach. *Eur J Cancer* 2001;37:2143–46.