Intraoperative radiotherapy for breast cancer

Jayant S Vaidya, Jeffrey S Tobias, Michael Baum, Mohammed Keshtgar, David Joseph, Frederik Wenz, Joan Houghton, Christobel Saunders, Tammy Corica, Derek D’Souza, Richard Sainsbury, Samuele Massarut, Irving Taylor, and Basil Hilaris

Postoperative radiotherapy, which forms part of breast-conserving therapy, may not need to encompass the whole breast. Apart from the consumption of huge resources and patients’ time, postoperative radiotherapy deters many women from receiving the benefits of breast-conserving surgery, forcing them to choose a mastectomy instead. If radiotherapy could be given in the operating theatre immediately after surgery, many of these disadvantages could be overcome. One striking fact about local recurrence after breast-conserving surgery is that most occurs in the area of breast immediately next to the primary tumour; this is despite the finding that two-thirds of mastectomy samples have microscopic tumours distributed throughout the breast, even when radiotherapy is omitted. Thus, only the area adjacent to the tumour may need treatment with radiotherapy. On the basis of this premise, clinical scientists have used new technology to administer radiotherapy to the area at greatest risk of local recurrence, with the aim of completing the whole local treatment in one sitting. In this review, we have elaborated on the rationale and different methods of delivery of intraoperative radiotherapy. If this approach is validated by the results of current randomised trials, it could save time, money, and breasts.

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Breast-conserving surgery followed by a 6-week course of postoperative radiotherapy (breast-conserving therapy) is now considered to be an equivalent therapy to mastectomy and is the current standard of care for patients with early operable breast cancer. This conservative approach still has the same radical intent as the destructive surgery first done by William Halstead over 100 years ago. Thus, without a real change in paradigm, we have a paradoxical picture in which tumours are diagnosed at earlier stages but are still treated with radical local treatment Here, we discuss the rationale and different methods of delivery of intraoperative radiotherapy. If this approach is validated by the results of current randomised trials, it could save time, money, and breasts.

JSV is a lecturer and JH is Director of the Clinical Trials Group; both in the Department of Surgery, Royal Free and University College Medical School, London, UK. MB is Professor Emeritus and IT is Professor of Surgery; both at University College, London, UK. JST is Professor of Radiation Oncology at the Myerstein Institute of Oncology, MK and RS are senior lecturers, and DD is a senior physicist; all at Middlesex Hospital, London, UK. DJ is a consultant radiation oncologist, CC is a consultant surgeon, and TC is Trials Coordinator; all at Sir Charles Gardiner Hospital, Perth, Australia. FW is Professor of Radiation Oncology at the University of Mannheim, Germany. SM is a consultant surgeon at the Centro di Riferimento Oncologico, Aviano, Italy. BH is Professor of Radiation Oncology at Our Lady of Mercy Medical Center, New York Medical College, NY, USA.

Correspondence: Dr Jayant S Vaidya, Department of Surgery, Royal Free and University College Medical School, Charles Bell House, 67–73 Riding House Street, London W1W 7EJ, UK. Tel: +44 (0) 7801 418072. Fax: +44 (0) 8701 307403. Email: j.vaidya@ucl.ac.uk
Patients with early local recurrence have a poor prognosis,4 psychological morbidity and induces a sense of failure. These associations suggest that angiogenesis.7,8 Young age (about 45 years or younger) is thought to be a risk factor for local recurrence after breast-conserving therapy,9 and radiotherapy seems to have a differential effect.10 Young age (about 45 years or younger) is thought to be a risk factor for local recurrence after breast-conserving therapy, and radiotherapy seems to have a differential effect.10

Cause of local recurrence and rationale for intraoperative radiotherapy

Although local recurrence may be only an indicator and not the determinant of distant relapse,4 it causes much psychological morbidity and induces a sense of failure. Patients with early local recurrence have a poor prognosis,1 which suggests that local recurrence arises from the seeding of circulating metastatic cells into a surgical field that is rich in growth factors. There is evidence that local recurrence is facilitated by a local field defect: morphologically normal cells that surround breast-cancer tissue show a loss of heterozygosity, which is in many cases identical to that of the primary tumour.5 In addition, aromatase activity is higher in the index quadrant than in other quadrants,6 and through the action of oestrogen has the potential to stimulate mutagenesis, growth, and angiogenesis.7 Young age (about 45 years or younger) is thought to be a risk factor for local recurrence after breast-conserving therapy; and radiotherapy seems to have a differential effect.8

Patients with ipsilateral breast-tumour recurrence are at a higher risk of having the mutated p53 gene (23% vs 1%)11 and young patients (<40 years) with ipsilateral breast-tumour recurrence have a disproportionately increased risk (40%) of carrying a deleterious BRCA1/2 mutation.8 These associations suggest that local recurrence is probably related more to background genetic instability than to a different tumour biology at a younger age. A dynamic interaction between local factors (such as aromatase) in the breast parenchyma, the systemic hormonal milieu, and genetic instability probably determines the risk of local recurrence, in addition to the biology of the excised primary tumour.

The location of recurrence in the breast with relation to the primary tumour site has an interesting distribution (table 1), between 80% and 100% of early breast recurrences occur in the quadrant that contained the primary tumour.4,5,6,7,8 By contrast, a whole-organ analysis of mastectomy samples done in three dimensions12 showed that 63% of breasts contain undetectable cancer foci, and 80% of these are situated remote from the index quadrant.

Table 1. Recurrences in large studies of breast conserving therapy

<table>
<thead>
<tr>
<th>Proportion of recurrences in index quadrant (%)</th>
<th>Number of patients</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>488</td>
<td>4</td>
</tr>
<tr>
<td>96</td>
<td>680</td>
<td>13</td>
</tr>
<tr>
<td>83</td>
<td>231</td>
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<td>81</td>
<td>783</td>
<td>15</td>
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<tr>
<td>86</td>
<td>1593</td>
<td>16</td>
</tr>
<tr>
<td>83</td>
<td>416</td>
<td>17 radiotherapy group</td>
</tr>
<tr>
<td>86</td>
<td>421</td>
<td>17 no radiotherapy group</td>
</tr>
<tr>
<td>90</td>
<td>570</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>5182</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Index-field interstitial brachytherapy series: patients with good outlook who are at low risk of local recurrence

<table>
<thead>
<tr>
<th>Institution</th>
<th>Radiotherapy technique</th>
<th>Median follow-up (years)</th>
<th>Crude local recurrence rate (actual numbers)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Oncology, Hungary</td>
<td>HDR</td>
<td>4·5</td>
<td>4·4% (2/45)</td>
<td>28</td>
</tr>
<tr>
<td>Ninewells Hospital, UK</td>
<td>LDR</td>
<td>5·6</td>
<td>0·0% (1/11)</td>
<td>30</td>
</tr>
<tr>
<td>Ochsen Clinic, USA</td>
<td>LDR or HDR</td>
<td>3·8</td>
<td>1·3% (2/150)</td>
<td>31</td>
</tr>
<tr>
<td>London Regional Cancer Centre, Canada</td>
<td>HDR</td>
<td>1·7</td>
<td>2·6% (1/39)</td>
<td>32</td>
</tr>
<tr>
<td>William Beaumont Hospital, USA</td>
<td>LDR or HDR</td>
<td>3·0</td>
<td>0·0% (1/174)</td>
<td>33</td>
</tr>
<tr>
<td>Orebro Medical Centre, Sweden</td>
<td>PDR</td>
<td>2·8</td>
<td>2·3% (1/43)</td>
<td>34</td>
</tr>
<tr>
<td>University of Kansas, USA</td>
<td>LDR</td>
<td>4·0</td>
<td>0·0% (1/24)</td>
<td>35</td>
</tr>
<tr>
<td>Tufts University, USA</td>
<td>HDR</td>
<td>2·0</td>
<td>0·0% (0/20)</td>
<td>36</td>
</tr>
</tbody>
</table>

HDR, high-dose rate; LDR, low-dose rate; PDR, pulsed-dose rate.

many countries can lead to long waiting lists, and a delay in delivery of radiotherapy (because of a long waiting time or because chemotherapy is given first) could jeopardise the effectiveness of radiotherapy and lose the window of opportunity. The externally delivered boost dose misses target volume in an estimated 24% to 88% of cases.21 Thus, a large proportion of local recurrences could be attributed to geographical miss alone.
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The radiation produced by Intrabeam induces both necrotic and apoptotic cell death, as well as rapid cell death through non-apoptotic pathways. Experiments with dogs showed that the ability of the photon radiosurgery system to ablate tumour tissue effectively has been shown by a series of three women with breast cancer (tumour size, 1.0–2.5 cm) treated with the photon radiosurgery system to ablate tumour tissue.41–43 The ability of the photon radiosurgery system to ablate tumour tissue effectively has been shown by a series of three women with breast cancer (tumour size, 1.0–2.5 cm) treated with the photon radiosurgery system 400 (bare probe only—ie, without the applicators but with the same Intrabeam machine used for intraoperative radiotherapy, see figure 2a). The patients in this series were too frail to have surgery. The tumour was localised by use of a digital stereotactic prone mammography table (called the Mammotest). The tip of the probe was placed in the centre of the tumour and radiation delivered over 6–12 min. The tumours were ablated with a single dose of radiotherapy as confirmed by examination of a biopsy sample and serial contrast-enhanced MRL.44

As yet, there are no firmly established standard intraoperative radiotherapy doses or schedules for use in early breast cancer. Intraoperative radiotherapy doses investigated for use in early breast cancer have ranged from 5 Gy to 22 Gy, given by various intraoperative radiotherapy systems. The IntraBeam intraoperative radiotherapy system delivers a physical dose of 5 Gy administered at a distance of 1 cm from the breast tumour cavity for 20–25 min, thought to be 35 min. Since healthy tissues can repair their DNA within a few minutes, a large proportion of radiation-induced DNA damage is repaired in healthy tissues during this long duration of intraoperative radiotherapy. However, cancer cells or precancerous cells with poor DNA-repair machinery are unable to do so. Thus, radiation given over 25–35 min by Intrabeam would have a high therapeutic index and would induce a lower amount of damage to healthy tissue than similar doses given over 2–3 min. Specific laboratory experiments to test this concept are currently being done.

**Dose attenuation in tissues**

The radiobiological effect of a single fraction of radiotherapy might be paradoxically higher at greater depth.37

Thus, the tissues immediately next to the applicator would have a high physical dose with a low therapeutic ratio, and tissues further away from the applicator would have lower physical dose but a high therapeutic ratio. Systems that use soft X-rays have a small high physical dose region and thereby offer an advantage over systems that use electrons to deliver a uniform dose of radiation: a high physical dose delivered over a small region would increase acute tumour effects while reducing damage to healthy tissue and long-term toxic effects.

**In vivo evidence of effectiveness**

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**Theoretical assumptions**

**Volume effect**

High single doses induce less damage to healthy tissues when given to a small volume. The theoretical basis for this is the Flickinger formula, which calculates the risk of brain necrosis when a single dose is administered to a defined volume. Such theoretical calculations accord very well with clinical experience. For example, single doses of 20–25 Gy can effectively sterilise brain metastases without inducing brain necrosis.

**Relative biological effect**

Low dose radiation has an increased relative biological effect. Radiobiological experiments with cell cultures have suggested that the relative biological effect of the Intrabeam system at 50 kV is between 1.2 and 2.5. This estimate accorded with microdosimetric analysis and modelling. Thus, the biological effects of cell killing extend further into the tissues than estimated from only the physical dose fall-off.

**Dose effect**

Single-dose radiation with Intrabeam (referred to as targeted intraoperative radiotherapy) is administered over 15 to 35 min. Since healthy tissues can repair their DNA within a few minutes, a large proportion of radiation-induced DNA damage is repaired in healthy tissues during this long duration of intraoperative radiotherapy. However, cancer cells or precancerous cells with poor DNA-repair machinery are unable to do so. Thus, radiation given over 25–35 min by Intrabeam would have a high therapeutic index and would induce a lower amount of damage to healthy tissue than similar doses given over 2–3 min. Specific laboratory experiments to test this concept are currently being done.
equivalent to a biologically effective dose of 21.7 Gy. Veronesi and co-workers used the Novac-7 intraoperative radiotherapy system to estimate that an external-beam dose of 60 Gy given in 30 fractions at 2 Gy per fraction is equivalent to a single intraoperative radiotherapy fraction of 20–22 Gy (with an $\alpha/\beta$ ratio at 10 Gy considered typical for tumours and acutely reacting tissues).\textsuperscript{45} With this same regimen, but when the tolerance of late-responding tissues ($\alpha/\beta$ ratio at 3 Gy) is taken into consideration, the equivalent value is at least 110 Gy. However, this equation may not be appropriate in the situation of single-fraction radiotherapy.

**The Intrabeam system**

On the basis of the hypothesis that index-quadrant irradiation is sufficient, in July, 1998, we introduced the technique of targeted intraoperative radiotherapy\textsuperscript{46} or radiotherapy delivered as a single dose by the use of low-energy X-rays, targeted at the tissues surrounding the tumour from within the breast by use of the Intrabeam device.\textsuperscript{47,48} In patients with small, well-differentiated breast cancers (now the most common form), this treatment could be the only radiotherapy that is required. In those with a high risk of local recurrence elsewhere in the breast (eg, lobular carcinoma and tumours with an extensive intraductal component), targeted intraoperative radiotherapy would avoid any geographical miss and, in combination with external-beam radiotherapy, might even reduce local recurrence.

The X-ray tube in the Intrabeam is powered by a 12 V supply, a miniature electron gun, and an electron accelerator. Radiation in the form of soft X-rays (low energy, 50 kV) is emitted from the point source and is modulated by spherical applicators to give a uniform dose of radiotherapy in a spherical field in the tumour bed. There is rapid attenuation of the radiation within tissues, which both reduces the damage to surrounding healthy tissues and limits the need for radiation protection of the operating personnel. Generally, the operating team leaves the room, but the anaesthetist and anyone who wants to observe the procedure sits behind the standard mobile lead shield where no harmful radiation is detectable. Various sizes of applicator spheres are available to match the size of the surgical cavity, and the amount of radiation received is proportional to the time the machine is switched on and left in situ. The precise dose depends on the diameter of the applicator and the energy of the beam, both of which can be changed to optimise the radiation treatment. For example, a dose of 5 Gy can be delivered in about 20 min at 1 cm from the margins of a 3.5 cm cavity after wide local excision of the tumour (figure 3).

If necessary, the chest wall and skin can be protected (95% shielding) by radio-opaque tungsten-filled polyurethane caps, which can be cut to size on the operating table—another advantage of use of soft X-rays. Rather elegantly, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source—ie, the target is conformed to the source (figure 4). This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of interstitial implantation of radioactive wires, or the even more complex techniques necessary for conformal radiotherapy by external beams with multileaf collimators from a linear accelerator. Use of soft X-rays eliminates geographical miss and delivers radiotherapy at the earliest possible time after surgery. The rapid attenuation of the radiation dose protects healthy tissues and allows the treatment to be done in unmodified operating theatres. Thus, in theory, the biological effect and cosmetic outcome could be improved.
185 patients undergoing breast-conserving surgery have been treated in pilot studies (median follow-up 22 months, maximum follow-up 58 months) in the UK, USA, Australia, Germany, and Italy with the Intrabeam to assess safety and feasibility. 163 patients received intraoperative radiotherapy in addition to external-beam radiotherapy as a substitute for the boost, and 22 patients received intraoperative radiotherapy as the only method of radiotherapy. Apart from two patients treated early in the study, wound healing was excellent. Two relapses occurred: one patient had a second primary tumour in a separate quadrant at 42 months, and a second patient had diffuse involvement of the whole breast 2 months after surgery. The cosmetic outcome was assessed in UK patients who were available at median follow-up of 42 months. The mean scores given by an independent surgeon and nurse for appearance, texture, and comfort of the breast were 3·5, 2·7, and 3·7, respectively (a score of 5 being the best). The corresponding scores given by the patients for appearance, texture, and comfort of the breast were 4·0, 3·1, and 3·5, respectively. Encouraged by these results, a randomised trial called Targit began in March 2000 in the UK and is now underway in Germany, Italy, the USA, and Australia.

The Novac-7 system
The Italian group (based in Milan) involved in the Targit trial is also testing targeted intraoperative radiotherapy, with the use of a mobile linear accelerator called the Novac-7 system (figure 5) in a randomised trial called ELIOT. Novac-7 is a mobile dedicated linear accelerator: its radiating head can be moved by an articulated arm that can work in an existing operating room. It delivers electron beams at four different nominal energies (3, 5, 7, and 9 MeV radiation). Beams are collimated by means of a hard-docking system, consisting of cylindrical perspex applicators available in different diameters. The source-to-surface distance is 80–100 cm. For radiation protection reasons, the system has a primary-beam stopper (which consists of a lead shield 15 cm thick) mounted on a trolley and three mobile barriers (100 cm in length, 150 cm in height, and 1·5 cm lead thickness). Electron beams that are delivered by Novac-7 have very high dose/pulse values compared with conventional linear accelerators.

Once the local resection has been done, the breast is mobilised from the pectoral muscle by 5–10 cm around the tumour bed and is separated from the skin by 3–5 cm in all directions. To limit irradiation to the thoracic wall, dedicated aluminium–lead discs (4 mm aluminium, 5 mm lead) of diameter 4–10 cm are placed between the deep face of the residual breast and the pectoralis muscle. The breast is then sutured to obliterate the tumour bed and bring the target tissues together. A needle and ruler measure the thickness of the target volume in at least three points, and this figure is averaged. The skin margins are stretched out of the radiation field by means of a device that consists of a metallic ring with four hooks. The cylindrical applicator (4–10 cm in diameter) is placed through the skin incision, and the source cylinder is docked onto the upper end of the applicator. Four barriers are placed to shield stray radiation, and all the personnel leave the operating room. Once the radiotherapy is finished, the wound is closed in the usual way.

Current randomised trials
The Targit randomised trial with the Intrabeam system is enrolling patients in centres in the UK, Europe, the USA, and Australia. The trial is designed to test the hypothesis that the strategy of targeted intraoperative radiotherapy in patients eligible for breast-conserving therapy with a facility to add whole-breast radiotherapy in patients at high risk of recurrence elsewhere in the breast (eg, lobular cancers or tumours with an extensive intraductal component) is equivalent to standard postoperative radiotherapy. In this pragmatic trial, each centre will have the facility to decide the degree of uncertainty. Therefore, the trial will be stratified according to each centre’s decision on which group of patients receive whole-breast radiotherapy in addition to the intraoperative radiotherapy dose. Endpoints include local recurrence, cosmetic outcome, patients’ satisfaction, and cost analysis. The first patient was enrolled in March, 2000, and the first results of this trial are expected to be available in 2007. The Milan trial with Novac-7 has also been recruiting...
since November, 2000, at a high rate, and its preliminary results are encouraging.

Health economics
Delivery of intraoperative radiotherapy with the Intrabeam extends the primary operation by about 15–45 min. In addition, 1–2 h of a radiotherapy physicist’s time is also required to prepare the device. By contrast, external-beam radiotherapy costs about 9 h for preparation, 6 h of radiotherapy-room time, and 30–60 h of patient’s time. If the cost of conventional radiotherapy is £2400, and only a 66% saving of preparation time is considered, intraoperative radiotherapy would save £1800 per patient. So, if we estimate that 25% of the 27 000 patients diagnosed with breast cancer each year in the UK are treated by conservative surgery and intraoperative radiotherapy, the new technique could potentially save about £13 million per year for the UK National Health Service. This estimate does not include the substantial saving of expensive resource time on linear accelerators (thereby reducing waiting lists) and more importantly the decreased time, effort, and inconvenience to patients. Thus, intraoperative radiotherapy, unlike many new treatments, could be actually less expensive than the current standard.

Conclusion
Local treatment of breast cancer has always included treatment of the whole breast with radical surgery or radiotherapy. This principle, which guided William Halsted in 19th century, causes overtreatment in the 21st century, for several reasons. First, the tumours now encountered are much smaller. Second, we have a better understanding of the biology of the disease. Third, and most importantly, although the breast parenchyma might have microscopic tumours in other quadrants, local recurrence occurs most commonly around the site of the primary tumour. This behaviour could allow us to target local therapy to the area around the primary tumour. Modern technology and miniaturisation has made possible the delivery of radiotherapy at the time of surgery in a standard operating theatre. In patients with a low risk of recurrence, intraoperative radiotherapy could be the only treatment necessary. In patients with high risk of recurrence, precise targeting of intraoperative radiotherapy might improve on the conventional external-boost treatment.

The new technology for intraoperative radiotherapy must first be tested in randomised trials before mere novelty and convenience dictate practice. Randomised trials are underway, comparing intraoperative radiotherapy with the usual 4–7 weeks of postoperative radiotherapy, in terms of achieving local control and cosmesis. The Targit trial is still open to participation from interested centres.

Search strategy
The terms “intraoperative”, “radiotherapy”, and “breast”, along with their derivatives were used to search PubMed and Web of Science’s Science Citation Index. All studies relating to intraoperative radiotherapy for breast cancer were included in the preparation of the review. No limitations were placed on language or year of publication.
Cancer centres could soon have a choice of several different techniques to provide local treatment for breast cancer that is most suited to their population of patients. Many more patients may be able to receive breast-conserving surgery without compromising oncological principles.

Acknowledgements
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Conflicts of interest
Carl Zeiss (who acquired the assets of Photoelectron Corporation, manufacturers of Intrabeam, after bankruptcy) provided travel support to JSV, MB, JH, and TC for attendance to various conferences and steering committee meetings.

References
Breast cancer radiotherapy

Review


Clinical picture

Bilateral pulmonary artery tumour emboli from renal carcinoma

Scott E Eggener and Daniel P Dalton

A 53-year-old male presented with shortness of breath and dyspnoea on exertion, which he noticed for several months. CT of the chest showed bilateral main pulmonary artery emboli with extension into the interlobar and segmental arteries, as well as several pulmonary infarcts (figure a). An abdominal CT scan showed a renal mass (9.8×8.6 cm) in the right kidney that extended into the inferior vena cava cranially to the level of the hepatic vasculature (figure b). A bilateral pulmonary embolectomy followed by a right nephrectomy with caval thrombectomy were done in the same surgical setting. A pathological review showed renal-cell carcinoma in samples of both the kidney and pulmonary artery. The patient’s recovery was uneventful and he was discharged from the hospital 8 days later, with plans to receive adjuvant interleukin-2 immunotherapy.

Correspondence: Dr Scott E Eggener, Northwestern Memorial Hospital, Suite 1303, 401 East Ontario Street, Chicago, IL 60611, USA. Tel: +1 312 664 8718. Fax: +1 312 926 3535. Email: eggeners@hotmail.com