

Commentary

Reducing radiotherapy dose in early breast cancer: the concept of conformal intraoperative brachytherapy

J S TOBIAS, FRCR, MD, J S VAIDYA, MS, FRCS, PhD, M KESHTGAR, FRCS, PhD, D P D'SOUZA, MSc, PhD
and M BAUM, MD, FRCS, FRCR

Meyerstein Institute of Oncology and Academic Department of Surgery, University College London Hospitals NHS Trust, London, UK

In *Time* magazine's extensively researched breast cancer issue (June 10, 2002), one particular quote had a special resonance for us. In the introduction to a remarkably comprehensive article, Dr Julie Gralow, an Oncologist at the Fred Hutchinson Cancer Research Centre in Seattle, stated "We may be far overtreating our patients... We've now got women being diagnosed with tumours that would probably never have been treated if we didn't have mammography. They probably would have lived long, natural, healthy lives never knowing they had breast cancer" (J Gralow, quoted in [1]).

For some years it has been apparent that, for many patients, powerful treatment by surgery (even when limited to tumour excision with breast preservation) together with a 6 week programme of radiation therapy may be more than sufficient. We already know a good deal (although not of course enough) about the profile of a typical breast cancer patient with low risk of local and distant recurrence: a small, low or moderate grade tumour, surgically completely excised, positive for oestrogen and/or progesterone receptors, negative for HER2 and with negative axillary nodes. Post-menopausal patients clearly have a lower incidence of local recurrence; for example, in the large study by Bartelink et al [2], patients over the age of 60 years had a rate of local recurrence following 50 Gy whole breast radiation of only 4% (without an additional boost), the rate reducing still further to 2.5% with an additional 16 Gy given by electron beam therapy. For patients aged 41 to 50 years, the rates were 9.5% and 5.8%, respectively (median follow-up 5.1 years). What's more, an ever increasing number of patients now present with small tumours (<1 cm) identified on mammographic screening, of whom approximately three-quarters will have oestrogen receptor (ER)/progesterone receptor (PR) positive tumours, for which targeted hormone therapy with tamoxifen offers sustained long-term benefit for both local and distant relapse [3, 4]. Using a well tolerated oral aromatase inhibitor such as Anastrozole reduces the risk still further (for both local and distant relapse), also, incidentally, reducing by three-quarters the risk of development of a contralateral primary breast cancer [5].

For all these reasons, we strongly support Gralow's view. Even in younger women known to be at higher risk of relapse, including those with axillary node-positive disease, the use of systemic adjuvant cytotoxics sharply

reduces the risk of recurrence [3, 4, 6]. For hormone receptor-positive patients, *i.e.* the large majority, adjuvant hormone therapy as well as surgical or medical oophorectomy all add further benefit [2–4, 6].

What is the consequence of Gralow's observation? In the past, it has been regarded as mere flight of fancy to imagine that we can identify patients at such low risk of recurrence that a less intensive form of treatment than local surgical excision followed by whole breast irradiation could be regarded as "adequate". In this sense, this general policy remains little different in principle from the equally compelling (in its day) policy of radical, then less damaging forms of mastectomy – although admittedly, using local excision, breast preservation and post-operative radiotherapy is generally regarded as more "humane" even though attempts at demonstrating an improved quality of life have been largely elusive [7]. None the less, the evolving history of local treatment for early breast cancer has centred on an ever increasing recognition of the importance of breast conservation for body image and cosmesis, an essential requirement for most women. This has largely been achieved by the increasing acceptance of breast-conserving surgery with post-operative radiotherapy [8]. Yet despite this ready acceptance, recent data from the world's largest ever randomized breast cancer study, with excellent quality control and a high level of expertise, confirm a mastectomy rate approaching 50% [ATAC Trialists Group, unpublished data].

We believe that the time has come to move on further. For many patients, particularly those presenting over the age of 50 years with small, low grade, ER positive, axillary node negative tumours, it is surely right to question the necessity of a lengthy and sometimes damaging course of radiation therapy. Radiation oncologists who are totally satisfied with their often excellent cosmetic results and low relapse rates following standard treatment should bear in mind the work of the Oxford-based Early Breast Cancer Trialists' Collaborative Group, namely that despite a lower breast cancer cause-specific death rate in irradiated patients, the increased mortality for other non-cancer causes wipes out this advantage [9]. The assumption that the excess non-cancer-related deaths in this large meta-analysis were due essentially to reliance on older outmoded radiation techniques may be correct – but it remains an assumption only, and considerable additional data attest to the cardiac, pulmonary and neurological dangers of whole breast irradiation [10–12]. Moreover, the use of anthracycline-based chemotherapy regimens apparently increases some of these risks still further [13].

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What about radiation dose and whole breast treatment? Most authorities recommend a standard dose of 50 Gy over a 5-week period with a boost for all patients, of up to 16 Gy. However, in the much criticized randomized study carried out in the 1960s by the Guy's group, even a low radiation dose to the whole breast, considered "inadequate" by today's standards, seemed to be sufficient for patients with axillary node-negative disease, *i.e.* with a low risk of local recurrence [14]. This was probably the earliest of prospectively randomized breast cancer studies comparing mastectomy (in this study radical mastectomy was still the standard surgical procedure, with formal axillary dissection) with wide local excision (often quadrantectomy) followed by radiation therapy. It was clear that for axillary node-positive patients, the low dose of radiation employed (38 Gy to the breast but only 27 Gy to the axilla) was insufficient; the overall survival was clearly worse in this group for patients treated by a breast-conserving surgical technique. However, in an important result often overlooked, the stage 1 patients (node negative) had an equally good survival prognosis whether subjected to radical mastectomy or treated by breast-conserving surgery with low dose radiation therapy. Yet another strand in the argument supporting Gralow's view, and was well established before the days of effective adjuvant systemic therapies that are clearly capable of reducing local recurrence still further.

Use of single fraction intraoperative irradiation at the time of initial surgical excision is attracting considerable interest. Not only *Time* but, more importantly, the Istituto Nazionale Milan, have recognized it as an important potential step forward, reducing the otherwise inevitable treatment delay between surgery and radiation therapy that patients (and staff in radiotherapy departments) find so unsettling. In Milan, use of *ELIOT* (Electron beam Intra-Operative radiation Therapy) employs a substantial electron-generating linear accelerator brought in a dedicated fashion to the operating room [15–17], but other techniques have also been employed. This group is now formally testing the intraoperative technique against conventional external beam radiation therapy in a prospective randomized study [18].

Our own approach has been to use the Intrabeam device, essentially a minaturized low energy photon generator, brought to the operating theatre at the time of surgery. The technique has been fully described [19, 20] and can be used both in conjunction with surgery or, alternatively, for frail patients whose general medical condition precludes either a general anaesthetic or major surgical procedure [21]. As part of the rationale for treating low-risk patients with intraoperative irradiation (without added external beam therapy), it is important to recall that most in-breast local recurrences following breast-conserving surgery occur within the index quadrant, despite the fact many breasts are known to harbour foci of other malignant sites (usually non-invasive) [22–25].

Methodology

The new radiotherapy technique: TARGED intraoperative radiotherapy (Targit)

We have previously published a pilot study carried out at University College London Hospitals. A novel method

of radiotherapy was used to deliver therapeutic radiation to the tissues around the primary tumour immediately following excision, with a degree of precision impossible with an external beam. The Photon Radiosurgery System (PRS), developed by the Photoelectron Corporation in Massachusetts, USA, is a simple and ingenious device, in essence a miniature electron beam-driven X-ray source providing a point source of low energy X-rays (50 kV maximum). The unit is connected, via a low voltage cable, to a control box housing a rechargeable NiCd battery. Within the unit itself, electrons are produced and accelerated to the desired energy by a multistage anode, and are directed down a 10 cm long, 3.2 mm diameter evacuated drift tube towards a thin-film hemispherical gold target at its tip. The radiation source can be inserted into the area of interest to provide intraoperative interstitial irradiation. The physics, dosimetry and early clinical applications of this soft X-ray device have been well studied and the probe has already been used for treatment of malignant brain tumours in man [26, 27], although treatment of breast cancer had not been previously attempted.

We regard this as a form of intraoperative conformal brachytherapy. For use in the breast, the radiation source is surrounded by a conical sheath with a sphere at the tip (see Figures 1–3). The sphere is specially designed to produce an accurately calculated uniform dose rate at its surface, enabling delivery of a uniform dose of radiation to a prescribed depth, with rapid attenuation of the beam to reduce the dose to more distant tissues. Depending upon the size of the surgical cavity, various sizes of applicator sphere are available and, for each size, the radiation received is proportional to the time the machine is switched on and left *in situ*. The precise dose rate

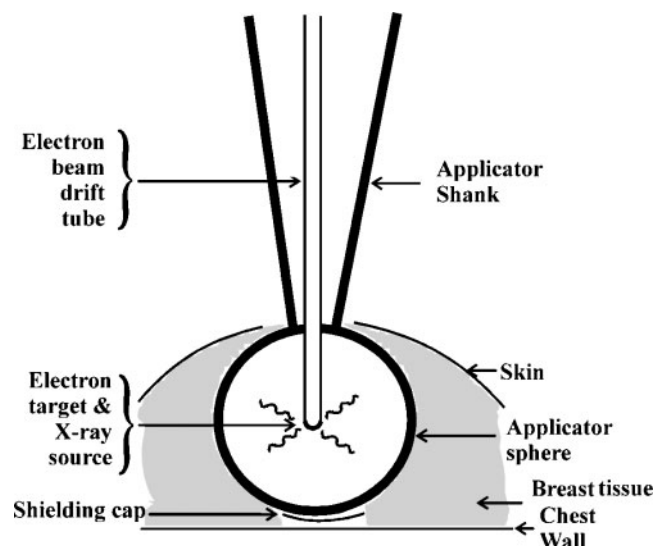


Figure 1. The Photon Radiosurgery system (PRS). The electrons are generated and accelerated in the main unit (seen in Figure 3) and travel via the electron beam drift tube, which is surrounded by the conical applicator sheath such that its tip lies at the epicentre of the applicator sphere. Once the electrons hit the inner surface of the hemisphere at the tip, X-rays are generated. Thus, a uniform radiation dose rate is available at the surface of the applicator sphere. There is a small, very high dose region close to the applicator, which attenuates quickly ($a \times 1/r^3$).

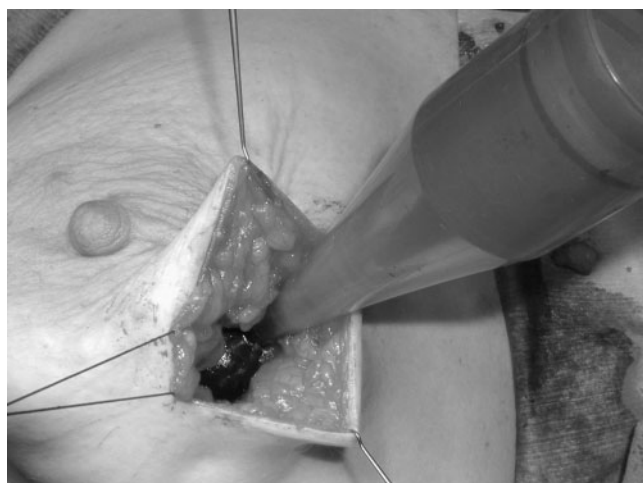


Figure 2. The applicator being placed in the tumour bed, immediately after excision of the tumour.

depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimize the radiation treatment. The radiation dose at various distances from the cavity margin varies as shown for the simulated assembly in Table 1. For example, a dose of

approximately 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. The whole assembly is small and lightweight (weight 1.8 kg; dimensions: X-ray generator body, 7 3/4 cm × 11 3/4 cm × 14 cm; applicator, 16 cm long conical applicator sheath with a 2–5 cm applicator sphere at the tip) and hangs dependently from a mobile gantry in perfect balance, remaining steady wherever it is positioned. If necessary, the chest wall and skin can be protected (95% shielding) by radio-opaque tungsten-filled polyurethane caps that can be cut to size on the operation table, another advantage of using soft X-rays. With this elegant approach, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source, *i.e.* the target is “conformed” to the source. This feature of the methodology represents a fundamental shift from more traditional forms of brachytherapy with wires, hairpins or radioactive seeds.

It also avoids the demanding complexity and attention to meticulous radiation protection of using interstitial of radioactive wires to provide high dose radiotherapy, or the equally challenging technique of conformal radiotherapy by external beams from a linear accelerator. The steep attenuation of the radiation dose allows the treatment to be carried out in unmodified operating theatres, whose

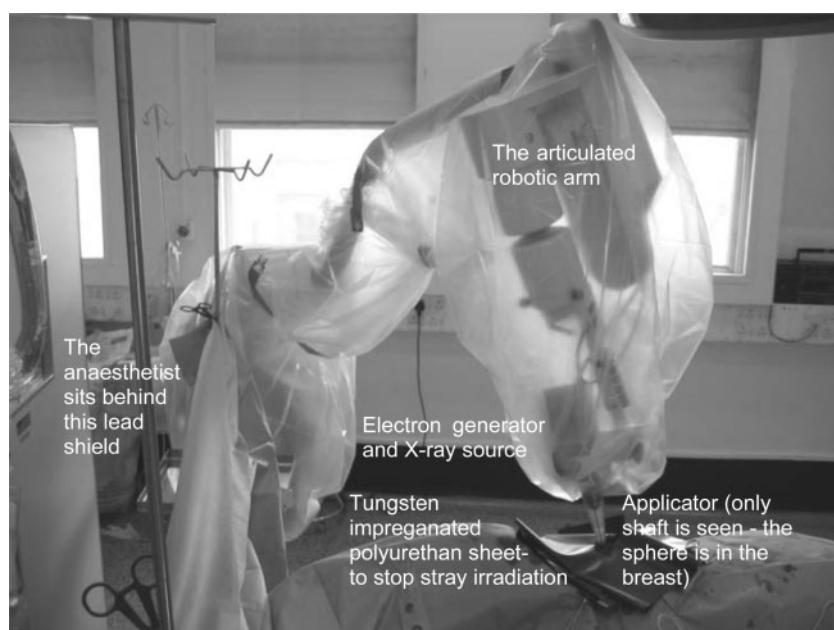


Figure 3. The Intrabeam system with the X-ray source in the breast wound and the electron generator and accelerator held by the articulated arm. Figure 2 demonstrates how the target breast tissue wraps around the applicator giving true conformal brachytherapy.

Table 1. Standard dosimetry table. Calculations for a 3.5 cm spherical diameter and a period of irradiation of 21 min as measured from the periphery of the sphere in a breast phantom. (Photon Radiosurgery System operating parameters: 50 kV.) Radial doses are stated for a treatment prescription of 5 Gy at 1 cm

Distance from the surface of the applicator (cm)	Intrabeam (Gy)		External beam radiotherapy tumour bed boost		Whole breast radiotherapy	
	Physical X-ray dose (Gy)	BED	Physical X-ray dose (Gy)	BED	Physical X-ray dose (Gy)	BED
0.1	15	165	10	12	50	60
0.2	12.5	121	10	12	50	60
0.5	8.75	59	10	12	50	60
1	5.0	21.7	10	12	50	60

Biologically effective dose (BED) is given by the equation [28]: $BED = D^{3/4} \{1 + [d/(a/b)]\}$, where D is the total physical dose, d is the physical dose per fraction and a/b is the biological coefficient, which is 10 for early and tumour effects for tumour tissues when the radiotherapy is delivered in fractions of approximately 2 Gy. For the single dose we have assumed the value of a/b to be equal to 1.5.

walls usually incorporate adequate shielding for microwave radiation from electronic equipment such as mobile phones, thus providing sufficient staff protection for the present purpose.

Results

We began the pilot study on 2 July 1998 and have treated 25 patients. All patients had early operable breast cancer, suitable for breast-conserving surgery. Ages ranged from 30–80 years (mean 51.5 years). Pathological tumour size ranged from 0.42–4.0 cm. 22 tumours were infiltrating duct carcinomas (4 Grade 1, 7 Grade 2 and 11 Grade 3), one was the tubular variant and three were invasive lobular carcinomas (two Grade 1 and one Grade 2).

22 patients had axillary node dissection and 3 patients had sentinel node biopsy only. All sentinel nodes were negative and three patients had involved lymph nodes (1, 2 and 1 node each). The applicator size was 3.5 cm in 13 cases, 4 cm and 4.5 cm in 4 cases each, 3 cm in 3 cases and 2.5 cm in 1 case. In all except the first case, the operating voltage was 50 kV at 40 mA. The mean treatment time required to treat the prescribed dose of 5 Gy at 1 cm was 26.5 min (95% confidence interval (95% CI); 24.3–28.8 min). The total mean operation time for the wide local excision, axillary clearance and intraoperative radiotherapy was 1 h 57 min (95% CI, 1 h 47 min–2 h 7 min). In the first case we used a 40 kV voltage and took 36.8 min.

Three patients received intraoperative radiotherapy as the only form of radiotherapy. One 80-year-old patient was blind and was keen to avoid daily post-operative visits for external beam radiotherapy. In a joint decision, she was prescribed 7.5 Gy (150% of the usual dose) at 1 cm, effectively giving approximately 23 Gy to the cavity margin as the only radiotherapy. Another patient had a contralateral breast cancer treated 14 years before, on that occasion with interstitial iridium wire boost and whole breast radiotherapy. In order not to overlap radiation beams in the midline, she was prescribed 6 Gy at 1 cm, giving 20 Gy to the cavity margin as the only radiotherapy. The third patient (patient 21 in the pilot study) was a lady who fully understood the rationale of our subsequent randomized study and chose not to undergo the 5-week course of whole breast radiotherapy, although we had not yet started the randomized trial to test this approach. All other patients received the routine external beam radiotherapy to the whole breast (50 Gy over 5 weeks). None has had major operative or post-operative complications either in general or in respect of the wound. Two patients had a delay in wound healing and one had wound infection. We believe that one of these was due to excessive radiation and radionecrosis. This was our third patient as mentioned before, who had radionecrosis of a 1 cm area of skin close to the applicator. The skin breakdown occurred 3 months after an initial good healing and resulted in delayed healing by secondary intention. In the 80-year-old blind patient, both the axillary (unirradiated site) and primary wound had delayed healing. Both these patients were very satisfied with the final appearance and/or texture of the breast. In the patient who developed a wound infection, the wound healed satisfactorily within 2 weeks without delay to her adjuvant treatment.

Some short-term erythema around the scar was seen in three patients.

The longest follow up is 5.5 years and median follow up is 4.5 years and a minimum of 4 years. One patient, who had received whole breast radiotherapy in addition to intraoperative radiotherapy developed a second tumour in a different quadrant at 42 months and remains well after mastectomy at 54 months.

Several centres in the USA, Australia, Germany and Italy have since performed pilot studies in over 200 patients with encouraging results.

Very few of the patients who were eligible (essentially all those who were suitable for breast-conserving therapy) have refused to participate in the study. Many found the technique appealing and logical, and could immediately see the practical advantage of fewer visits to the radiotherapy department. The concept of giving the radiotherapy to the tumour bed “there and then” was also very attractive. The cosmetic outcome (details being presented elsewhere) has also been good.

Discussion

For a variety of reasons, many hospitals in the UK and elsewhere are currently experiencing lengthening delays for patients who require radiotherapy. It is far from unusual for patients to be told that treatment cannot begin for 3 or 4 months or even longer. For younger women, either with positive axillary nodes or other features indicating a high risk of recurrence, initial treatment is likely to be with chemotherapy—in which case the patient can be sensibly booked in for radiotherapy at the outset of the programme, undergoing the radiotherapy itself at the appropriate time, after chemotherapy has been completed, typically 4 or 5 months after the first cycle.

The majority of patients, however, fall into the low risk category, or for other reasons cannot justifiably be recommended to undergo chemotherapy. This will include the majority of post-menopausal patients who, after all, still comprise 75% of all women we see. What of these? No scientifically justifiable treatment can be recommended between surgical excision (usually conservative, with breast preservation) and radiation therapy, although many are commenced during the interim period on adjuvant hormone therapy. For this large group, the use of immediate intraoperative conformal brachytherapy is especially attractive.

Since March 2000, we have been recruiting patients for a multicentre international randomized trial (TARGIT: TARGeted Intraoperative radioTherapy) [28] comparing conventional radiotherapy with radiotherapy delivered to the index quadrant alone, using the Intrabeam device. [protocol can be seen at <http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=99> 20]. This is a pragmatic multicentre trial, in which patients suitable for breast-conserving therapy undergoing wide local excision and axillary clearance will be randomized to receive either the intraoperative radiotherapy only, or the conventional extended course of post-operative radiotherapy. If on final histopathology, the tumour is found to be lobular cancer or to be harbouring an extensive intraductal component, patients will receive additional post-operative whole breast radiotherapy, excluding an additional tumour bed boost. In the pilot study we had only one patient with a positive margin—the deep margin. Since this was the

blind patient who had received the higher (7.5 Gy at 1 cm) dose of radiotherapy, the area adjacent to the tumour bed would have received approximately 23 Gy, which was thought to be adequate. A decision to give no further treatment was taken jointly in our multidisciplinary meeting and with the patient, and the tumour has not recurred. In the randomized trial, the protocol includes a provision to re-excise the tumour in patients with grossly positive margins, and to re-irradiate the revised tumour bed if they were randomized to the intraoperative radiotherapy arm. Previous intraoperative radiotherapy should not be a contraindication, because the previously irradiated area would have been excised in the re-excision. Alternatively, since these patients will fall in the group with high risk of local recurrence, they should receive whole breast radiotherapy.

Over 100 patients have already been randomized and over 15 centres from around the globe are expected to participate.

Clearly a substantial multicentre randomized study is the only means of confirming whether or not this exciting new treatment will prove adequate, but the many potential advantages make such a trial essential. These advantages include: immediate treatment with radiotherapy at the time of surgery; accuracy of locating the radiation at the site of the tumour bed (currently guesswork for most patients using conventional external boosts—see, for example, [29]); elimination of a lengthy treatment programme for a large proportion of women with breast cancer; and a freeing up of precious resources in oncology departments, thereby allowing general waiting lists for other urgent indications to fall sharply. Furthermore, many patients still have little access to breast-preserving treatment because of the demands of such lengthy radiation programmes—not only in developing countries, but even closer to home. Patients most likely to benefit and prove suitable include those diagnosed in the post-menopausal age group with small, low or moderate grade ER-positive tumours with only a small risk of local recurrence. These comprise a substantial proportion of the patients we see. We urgently need to know whether Dr Gralow is right in her contention that many patients with breast cancer are grossly overtreated, but we think she is. The medical and economic implications flowing from this insight are considerable, since treatment of breast carcinoma often represents one-third or more of the total caseload of radiotherapy units worldwide. Many women from the developing world and remote areas of the developed world (e.g. distant rural areas of Australia or India) cannot benefit from breast-conserving therapy because of the large distances between their home and the radiotherapy centre. All too frequently they have to choose mastectomy because they cannot stay in or travel daily to the metropolis for the 6 weeks of post-operative radiotherapy.

If proven equal to the standard approach, the novel technique would allow these women to have breast-conserving therapy at one sitting. In terms of operational expenses, the novel technique needs about 3 man-hours and 45 min each of operation theatre time and patient time. The conventional 6-week course of post-operative radiotherapy, on the other hand, costs about 9 man-hours, 6 hours of radiotherapy room time and 30–60 hours of patient time. If the cost of conventional radiotherapy is of the order of £5000, then considering only the 66% saving

of man-hours, the novel technique would save £3750 per patient. Furthermore, if we assume that 60% of the 27 000 breast cancer patients diagnosed every year in the UK could be treated by conservative surgery, the novel technique might potentially save over £60 million ($0.60 \times 27000 \times 3750$) per year for the NHS. In addition, the saving of expensive resource time on linear accelerators would of course be very substantial. Food for thought!

Conflict of interest

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References

1. Gorman C. Rethinking breast cancer. *Time Magazine* 2002;159:46–54.
2. Bartelink H, Horiot J-C, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; 345:1378–87.
3. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trial. *Lancet* 1998;351:1451–67.
4. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930–42.
5. Baum M, Buzdar UA, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T. ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131–9. [Erratum. *Lancet* 2002;360: 1520.]
6. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women (part I). *Lancet* 1992;339:1–15.
7. Fallowfield LJ, Baum M, Maguire GP. Effects of breast conservation on psychological morbidity associate with diagnosis and treatment of breast cancer. *Br Med J* 1986; 293:1331–4.
8. Tobias JS. Radiotherapy and breast conservation. *Br J Radiol* 1986;59:653–66.
9. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000;355:1757–70.
10. Rutqvist LE, Johansson H. Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry. *Br J Cancer* 1990;61:866–8.
11. Lind PA, Gagliardi G, Wennberg B, Fornander T. A descriptive study of pulmonary complications after post-operative radiation therapy in node-positive stage II breast cancer. *Acta Oncol* 1997;36:509–15.
12. Royal College of Radiologists. Report of the Independent Review Commissioned by The Royal College to Brachial plexus neuropathy following radiotherapy for breast carcinoma. Independent Review. [eds T Bates and R G B Evans]. London: Royal College of Radiologists, 1995.
13. Meinardi MT, van Veldhuisen DJ, Gietema JA, et al. Prospective evaluation of early cardiac damage induced by epirubicin containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. *J Clin Oncol* 2001;19:2746–53.

14. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment for early breast cancer: a report after ten years of a clinical trial. *Br Med J* 1972;2:423–9.
15. Orecchia R, Veronesi U. The Milan Trial. 3rd European Breast Cancer Conference; Barcelona; March 2002. *Eur J Cancer* 30; Suppl. 3:S90 (abstract 193).
16. Veronesi U. Intraoperative radiotherapy: rationale, techniques, results. Proceedings, 3rd European Breast Cancer Conference, Barcelona, March 2002: *Eur J Cancer* 38; Suppl. 3:S89 (abstract 190).
17. 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.
18. Veronesi U, Vicini F, Orecchia R. Highlights of surgery and radiotherapy. *The Breast* 2002;11:194–5.
19. Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit). *Ann Oncol* 2001;12:1–6.
20. Vaidya JS, Baum M, Tobias JS, et al. The novel technique of delivering targeted intra-operative radiotherapy (Targit) for early breast cancer. *Eur J Surg Oncol* 2002;28:447–54.
21. Vaidya JS, Hall-Craggs M, Baum M, Tobias JS, et al. Percutaneous minimally invasive stereotactic primary radiotherapy for breast cancer. *Lancet Oncol* 2002;3:252–3.
22. Vaidya JS, Vyas JJ, Chinoy RF, et al. Multicentricity of breast cancer: whole organ analysis and clinical implications. *Br J Cancer* 1996;74:820–4.
23. Vaidya JS, Baum M, Tobias JS, et al. Targeted intraoperative radiotherapy for breast cancer (Targit)—a randomised trial. *Breast Cancer Res Treat* 2001;69:145.
24. Vaidya JS, Baum M. Clinical and biological implications of the Milan breast conservation trials. *Eur J Cancer* 1998;34:1143–4.
25. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. *Lancet* 1997;349:208.
26. Cosgrove GR, Hochberg FH, Pardo FS, et al. Interstitial irradiation of brain tumors using a miniature radiosurgery device: initial experience. *Neurosurgery* 1997;40:518–25.
27. Douglas RM, Beatty J, Gall K, et al. Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases. *Int J Radiat Oncol Biol Phys* 1996;36:443–50.
28. Vaidya JS, Tobias JS, Houghton J, Joseph D, Wenz F, Hilaris BS, et al. Intra-operative breast radiation: the targeted intraoperative radiotherapy (Targit) trial. *Br Cancer Res Treat* 2003;82(Suppl. 1):S2–S3.
29. Doleckova M. The problem of the planning of electron boost in breast cancer. Presented at ISRO 2001, Melbourne, Australia.