Intraoperative radiotherapy for breast cancer

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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 for change in the treatment of early operable breast cancer and present ways in which change can be implemented, such as through the technique of intraoperative radiotherapy (figure 1).

Furthermore, although the concept of breast-conserving surgery has been established for more than a decade, numbers of mastectomies are still very high. Local culture, distance from a radiotherapy facility, surgeon's choice, and patient's preference all influence which operation is chosen.

The main obstacle to wider acceptance of breast-conserving surgery is the dogma of 6 weeks of postoperative radiotherapy, which has several disadvantages: first, the long course of treatment is a substantial burden on women, especially after a 6-month course of chemotherapy; second,

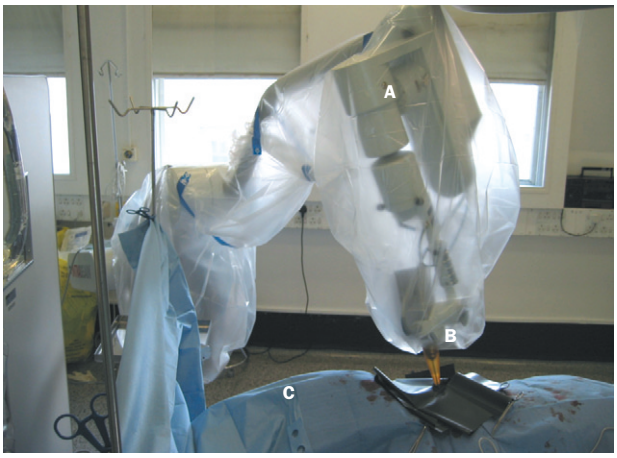

Figure 1. The Intrabeam system. An X-ray source is placed in the breast wound; an electron generator and accelerator are held by an articulated robotic arm (a). Only the shaft of the applicator (b) can be seen; the tip of the device is in the breast tissue. A tungsten-impregnated polyurethane sheet is used to localise irradiation (c).

many women are forced to choose a mastectomy because they live too far away from a radiotherapy facility or have difficulty travelling to one. Problems relating to distance are not restricted to developing countries. A study in the USA found that the further away the patient lives, the less likely she is to receive breast-conserving therapy and radiotherapy after breast-conserving surgery: the proportion of women receiving radiotherapy after breast-conserving surgery was 82% if the travel distance was less than 10 miles (16 km), 69% for 50–75 miles, and 42% for more than 100 miles.[1] Therefore, many women may be receiving suboptimum treatment. Furthermore, scarce radiotherapy resources in

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Table 1. Recurrences in large studies of breast conserving therapy

Proportion of recurrences in index quadrant (%)	Number of patients	Ref
100	488	4
96	680	13
83	231	14
81	783	15
86	1593	16
83	416	17 (radiotherapy group)
86	421	17 (no radiotherapy group)
90	570	18
Total		
91	5182	

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.[2,3] Thus, a large proportion of local recurrences could be attributed to geographical miss alone.

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,[4] 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.[7,8] 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]

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.[12] 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.[4,13–18] By contrast, a whole-organ analysis of mastectomy samples done in three dimensions[19] showed that 63% of breasts contain undetectable cancer foci, and 80% of these are situated remote from the index quadrant.

These widespread and undetectable multifocal or multicentric cancers in other quadrants of the breast are likely to remain dormant for a long time and to have a low risk of causing clinical tumours. This idea is supported by the fact that, although there is a high frequency of tumours found in breasts when analysed in autopsy studies (20% in young women of median age of 39 years and 33% in women aged 50–55 years),[20] the frequency of clinical breast cancer in the population is much lower (about 8% lifetime risk in a population undergoing mammographic screening).

Bartelink and colleagues[21] reported that only 56% of local recurrences occurred in the original tumour bed. In addition, 27% occurred diffusely throughout the breast including the tumour bed (ie, 29% recurrence outside the index quadrant). However, patients in that study received intensive mammographic follow-up that could have identified subclinical tumours in other quadrants with unproven clinical improvement.

Local recurrence probably occurs in the index quadrant, irrespective of whether radiotherapy is given[13,17,22] and irrespective of clear margins. Of the breast-conserving trials that have tested the effect of radiotherapy, the NSABP-B06,[23] Ontario,[24] Swedish,[25] and Scottish[26] trials had less extensive surgery than the Milan III trial.[18] The recurrence rate in patients in the control group of the Milan III trial—in which the tumours were smaller and the amount of tissue excised

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

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

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

much wider—was low (9% *vs* 24–27% in other trials) but occurred at the cost of cosmetic appearance. Nevertheless, radiotherapy reduced recurrence even further and at the same rates over time as the trials that excised a much smaller volume of breast tissue. If local recurrence was caused by residual disease only, radiotherapy should lead to a much larger proportional reduction in patients with positive margins or less extensive surgery; but the finding that radiotherapy is as effective in patients with negative margins suggests that radiotherapy has an effect on the peritumoural breast tissue rather than precancerous cells (akin to changes in the "soil" rather than the "seed" in the soil and seed hypothesis that defines the provision of an adequate microenvironment to allow the development of metastases from disseminated tumour cells.)

Thus, radiotherapy could inhibit the growth of genetically unstable cells around the primary tumour and make the whole breast tissue less conducive to growth. Systemic therapies such as aromatase inhibitors or ovarian suppression might achieve the latter effect through a reduction of oestrogen concentration in the breast. Therefore, with increasing use of systemic therapy, radiotherapy to just the tissues surrounding the primary tumour might be adequate. Such an approach could solve many problems associated with postoperative radiotherapy and might increase the numbers of patients who receive breast-conserving surgery, allowing many more women with breast cancer to conserve their breasts.

Irradiation of the index quadrant alone has been tested in the Christie Hospital trial[27] and, contrary to popular belief, the findings are encouraging. 708 patients were randomly assigned either standard wide-field radiotherapy or a limited-field radiotherapy to the index quadrant. Overall, there were more recurrences in the limited-field group. In that group, a constant size of radiotherapy field was used (irrespective of the tumour size), which could have resulted in several instances of geographical misses. More importantly, when the results were analysed according to the type of the primary tumour, limited-field radiotherapy was inadequate only in infiltrating lobular cancers or cancers with an extensive intraductal component. In the 504 cases of infiltrating-duct carcinoma, there was no considerable difference in the local-recurrence rates of the two groups of patients.

Brachytherapy

When patients with small infiltrating-duct cancers and uninvolved nodes are given interstitial brachytherapy by means of catheters and radioactive sources, local recurrence is between 0% and 4% at 2–5-year's follow-up (table 2). We should emphasise that the patients in these series had small tumours and a low risk of local recurrence. In a randomised trial in 2002,[28,29] brachytherapy was equivalent to whole-breast radiotherapy at 30-month's follow-up. This result provides further evidence for the treatment of the index quadrant. These studies used standard high-dose brachytherapy delivered with a radioactive source (iridium, caesium, or radioactive pellets within a saline-filled balloon) placed intraoperatively to cover a large field in the breast. These techniques require after-loading of the radioactive source in the catheter or balloon templates. Typically, this is done in five to ten fractions delivered in the postoperative period, over 4–5 days. This treatment technique is fundamentally and conceptually different from intraoperative radiotherapy, which is delivered as a single dose at the time of primary surgery (although it does share the basic premise of treating only the index quadrant).

Table 3. Characteristics of intraoperative radiotherapy systems

Device	Radiation type	Dose	Weight of treatment device
Intrabeam	Soft X-rays at 50 kV	Typical physical dose of 5 Gy at 1 cm, 10 Gy at 0·5 cm, or 20 Gy next to applicator over 25–30 min Set-up time is about 10–12 min	1·8 kg
Mobetron	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min Set-up time is about 20 min	1275 kg
Novac-7	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min Set-up time is about 20 min	650 kg

Techniques of intraoperative radiotherapy

Older intraoperative radiotherapy devices are technically cumbersome. The devices commonly rely on the transportation of the patient from the operating theatre to the radiotherapy unit during surgery, or require custom-built intraoperative radiotherapy theatres. These technical and financial limitations to delivery of intraoperative radiotherapy have prevented widespread use of the approach.

Advances in miniaturisation technology have enabled the development of mobile intraoperative radiotherapy devices. Intraoperative radiotherapy was first used in 1998 with a device called the Intrabeam. Since then, two other mobile linear accelerators have become available (the Mobetron and Novac-7 systems). Table 3 shows the characteristics of these machines.

Radiobiology of intraoperative radiotherapy

Whether a single dose of intraoperative radiotherapy has an identical biological effect on tissue to a full course of fractionated external-beam radiotherapy has not been proven. Generally, radiation oncologists fear the risk of increased occurrence of late effects when high single doses of radiation are given, especially when late-reacting tissues are involved. However, there is already some evidence for the safety and effectiveness of a single dose of radiotherapy in achieving tumour-cell death.

The theoretical basis for the calculation of the biological effects of a given dose of radiation is the linear-quadratic model. This model is based on the different shapes of cell-survival curves produced by acutely reacting and late-reacting tissues. Large single doses of radiation are assumed to be more effective on late-responding tissues than on acutely reacting tissues. However, the linear-quadratic model is reliable only for single doses up to 6–8 Gy, and

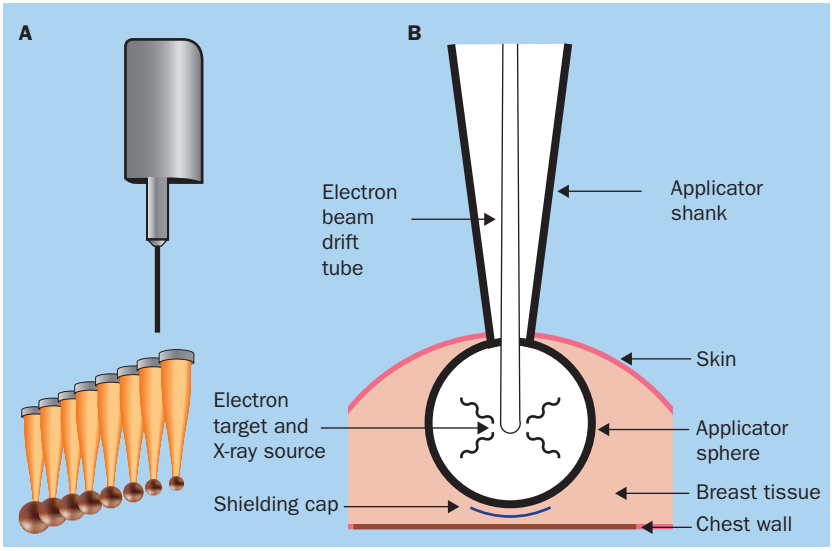

Figure 2. (a) The Intrabeam X-ray source (upper) and applicators (lower). (b) Schematic diagram showing how target tissues are irradiated from within the breast and how intrathoracic structures can be protected with a thin shield.

therefore might not be appropriate for modelling the effects of higher single doses (20–25 Gy) used in intraoperative radiotherapy or radiosurgery. Furthermore, volume, relative biological effect, and dose are important factors peculiar to intraoperative radiotherapy (especially with the Intrabeam system) and are not accurately represented in the standard model calculations.

To estimate the biological effects induced by intraoperative radiotherapy with the Intrabeam system, some theoretical assumptions can be made and clinical analogies drawn.

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 idea 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[37] 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.[38] 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[39]) 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.

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

The radiation produced by Intrabeam induces both necrotic and apoptotic cell death, as well as rapid cell death through non-apoptotic pathways.[40] Experiments with dogs showed that use of the photon radiosurgery system can lead to accurately demarcated ablation in the liver and kidney.[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, 1·0–2·5cm) 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 MRI.[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

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 α/β ratio at 10 Gy considered typical for tumours and acutely reacting tissues).[45] With this same regimen, but when the tolerance of late-responding tissues (α/β ratio at 3 Gy) is taken in to 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[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.[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.

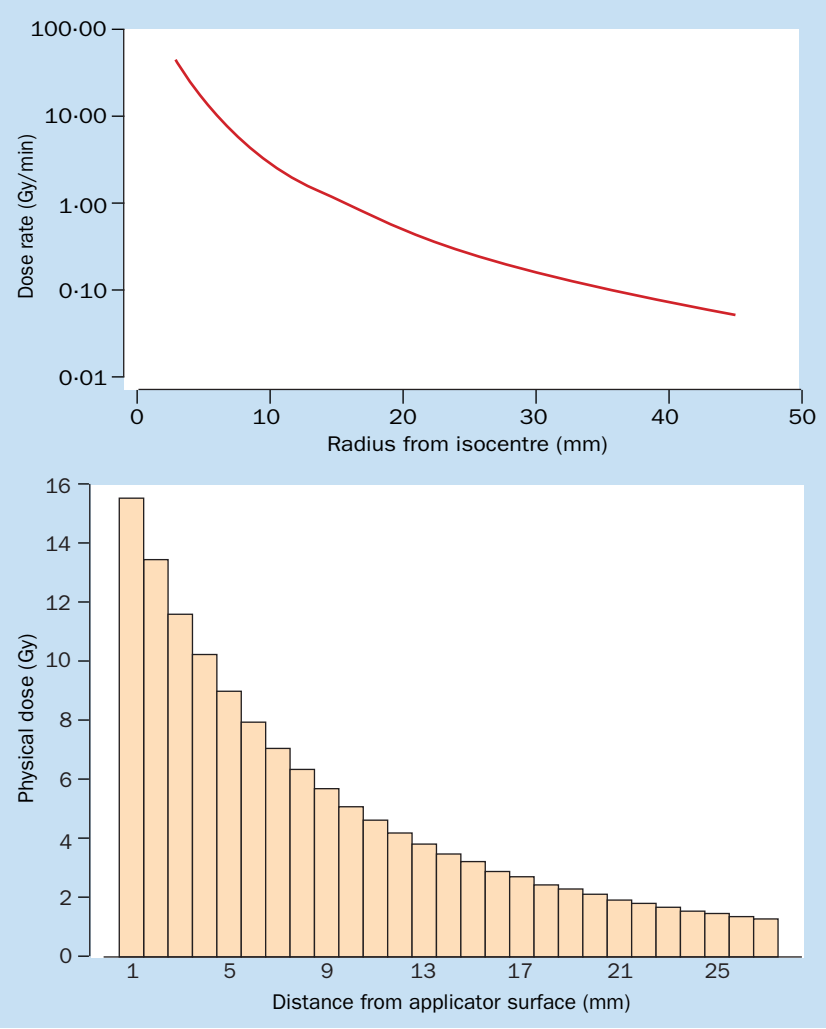

Figure 3. Intrabeam: dosimetry around the bare probe in water (upper) and around a 3·5 cm applicator in a phantom breast (lower). Physical dose was done with 5 Gy at 1 cm.

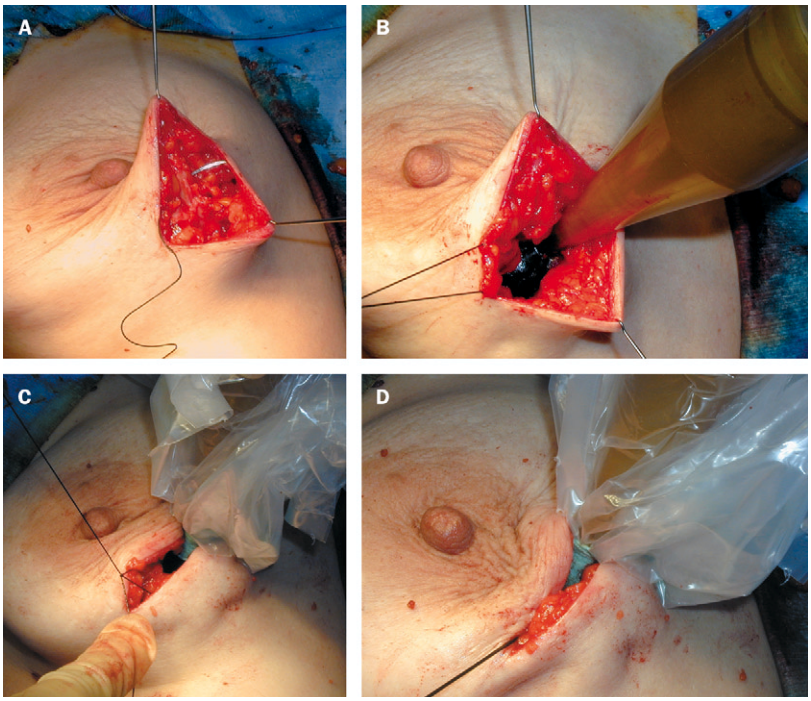

Figure 4. After wide local excision of the primary tumour (a), the applicator is inserted into the tumour bed (b). The applicator is secured with a purse-string suture (c) so that the target breast tissue wraps around the applicator, giving true conformal brachytherapy (d).

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[49] 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[39,50] 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,[45,51] 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

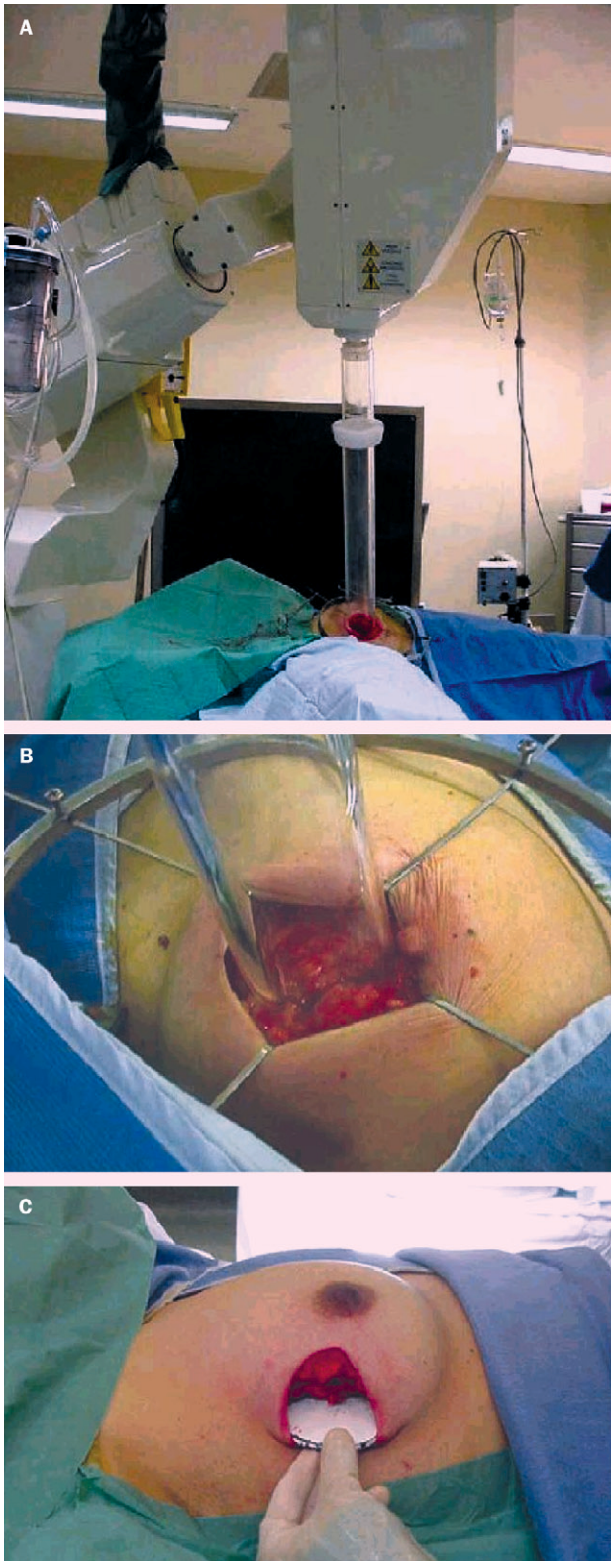

Figure 5. The Novac-7 system. (a) The arm of the mobile linear accelerator is attached to a perspex cylinder that is introduced in the breast wound (b). The breast tissue is mobilised from the chest wall and overlying skin, and apposed in the wound after placing a lead shield between the breast and pectoralis muscle (c). Reproduced with permission from reference 45.

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.

Acknowledgments

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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

1 Athas WF, Adams-Cameron M, Hunt WC, et al. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 2000; **92:** 269–71.
2 Sedlmayer F, Rahim HB, Kogelnik HD, et al. Quality assurance in breast cancer brachytherapy: geographic miss in the interstitial boost treatment of the tumor bed. *Int J Radiat Oncol Biol Phys* 1996; **34:** 1133–39.
3 Machtay M, Lanciano R, Hoffman J, Hanks GE. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994; **30:** 43–48.
4 Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Semin Surg Oncol* 1992; **8:** 161–66.
5 Deng G, Lu Y, Zlotnikov G, et al. Loss of heterozygosity in normal tissue adjacent to breast carcinomas. *Science* 1996; **274:** 2057–59.
6 O'Neill JS, Elton RA, Miller WR. Aromatase activity in adipose tissue from breast quadrants: a link with tumour site. *BMJ (Clin Res Ed)* 1988; **296:** 741–3.
7 Nakamura J, Savinov A, Lu Q, Brodie A. Estrogen regulates vascular endothelial growth/permeability factor expression in 7,12-dimethylbenz(a)anthracene-induced rat mammary tumors. *Endocrinology* 1996; **137:** 5589–96.
8 Lu Q, Nakmura J, Savinov A, et al. Expression of aromatase protein and messenger ribonucleic acid in tumor epithelial cells and evidence of functional significance of locally produced estrogen in human breast cancers. *Endocrinology* 1996; **137:** 3061–68.
9 Harrold EV, Turner BC, Matloff ET, et al. Local recurrence in the conservatively treated breast cancer patient: a correlation with age and family history. *Cancer J Sci Am* 1998; **4:** 302–07.
10 Arriagada R, Le MG, Contesso G, et al. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. *Ann Oncol* 2002; **13:** 1404–13.
11 Turner BC, Gumbs AA, Carbone CJ, et al. Mutant p53 protein overexpression in women with ipsilateral breast tumor recurrence following lumpectomy and radiation therapy. *Cancer* 2000; **88:** 1091–98.
12 Turner BC, Harrold E, Matloff E, et al. BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast-conserving management in patients with BRCA1/BRCA2 mutations. *J Clin Oncol* 1999; **17:** 3017–24.
13 Clark RM, Wilkinson RH, Mahoney LJ, et al. Breast cancer: a 21 year experience with conservative surgery and radiation. *Int J Radiat Oncol Biol Phys* 1982; **8:** 967–79.
14 Schnitt SJ, Connolly JL, Harris JR, et al. Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer* 1984; **53:** 1049–57.
15 Boyages J, Recht A, Connolly JL, et al. Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* 1990; **19:** 29–41.
16 Kurtz JM, Amalric R, Brandone H, et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 1989; **63:** 1912–17.
17 Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 1992; **84:** 683–89.
18 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.
19 Vaidya JS, Vyas JJ, Chinoy RF, et al. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 1996; **74:** 820–04.
20 Nielsen M, Thomsen JL, Primdahl S, et al. Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *Br J Cancer* 1987; **56:** 814–19.
21 Bartelink H, Horiot JC, 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.
22 McCulloch PG, MacIntyre A. Effects of surgery on the generation of lymphokine-activated killer cells in patients with breast cancer. *Br J Surg* 1993; **80:** 1005–07.
23 Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995; **333:** 1456–61.
24 Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996; **88:** 1659–64.
25 Liljegren G, Holmberg L, Bergh J, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999; **17:** 2326–33.
26 Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996; **348:** 708–13.
27 Ribeiro GG, Magee B, Swindell R, et al. The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol* 1993; **5:** 278–83.
28 Polgar C, Sulyok Z, Fodor J, et al. Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: five-year results of a phase I-II study and initial findings of a randomized phase III trial. *J Surg Oncol* 2002; **80:** 121–28.
29 Polgar C, Fodor J, Major T, et al. Radiotherapy confined to the tumor bed following breast conserving surgery current status, controversies, and future projects. *Strahlenther Onkol* 2002; **178:** 597–606.
30 Samuel LM, Dewar JA, Preece PE, Wood RAB. A pilot study of radical radiotherapy using a perioperative implant following wide local excision for carcinoma of the breast. *Breast* 1999; **8:** 95–97.
31 King TA, Bolton JS, Kuske RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000; **180:** 299–304.
32 Perera F, Engel J, Holliday R, et al. Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: a pilot study. *J Surg Oncol* 1997; **65:** 263–67.
33 Vicini FA, Baglan KL, Kestin LL, et al. Accelerated treatment of breast cancer. *J Clin Oncol* 2001; **19:** 1993–2001.
34 Johansson B, Karlsson L, Liljegren G. PDR brachytherapy as the sole adjuvant radiotherapy after breast conserving surgery for T1–2 breast cancer. Proceedings of the 10th International Brachytherapy Conference, Madrid, 2000: 127 (abstr).
35 Krishnan L, Jewell WR, Tawfik OW, Krishnan EC. Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. *Breast J* 2001; **7:** 91–96.
36 Wazer DE, Lowther D, Boyle T, et al. Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2001; **50:** 107–11.
37 Astor MB, Hilaris BS, Gruerio A, et al. Preclinical studies with the photon radiosurgery system (PRS). *Int J Radiat Oncol Biol Phys* 2000; **47:** 809–13.
38 Brenner DJ, Leu CS, Beatty JF, Shefer RE. Clinical relative biological effectiveness of low-energy x-rays emitted by miniature X-ray devices. *Phys Med Biol* 1999; **44:** 323–33.
39 Vaidya JS, Baum M, Tobias JS, Houghton J. Protocol 99PRT/47 targeted intraoperative radiotherapy (Targit) for breast cancer. http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=9920, accessed Jan 2004.

40 Kurita H, Ostertag CB, Baumer B, et al. Early effects of RS-irradiation for 9L gliosarcoma: characterization of interphase cell death. *Minim Invasive Neurosurg* 2000; **43:** 197–200.
41 Chan DY, Koniaris L, Magee C, et al. Feasibility of ablating normal renal parenchyma by interstitial photon radiation energy: study in a canine model. *J Endourol* 2000; **14:** 111–16.
42 Koniaris LG, Chan DY, Magee C, et al. Focal hepatic ablation using interstitial photon radiation energy. *J Am Coll Surg* 2000; **191:** 164–74.
43 Solomon SB, Koniaris LG, Chan DY, et al. Temporal CT changes after hepatic and renal interstitial radiotherapy in a canine model. *J Comput Assist Tomogr* 2001; **25:** 74–80.
44 Vaidya JS, Hall-Craggs M, Baum M, et al. Percutaneous minimally invasive stereotactic primary radiotherapy for breast cancer. *Lancet Oncol* 2002; **3:** 252–53.
45 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.
46 Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001; **12:** 1075–80.
47 Vaidya JS, Baum M, Tobias JS, et al. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *Eur J Surg Oncol* 2002; **28:** 447–54.
48 Vaidya JS. A novel approach for local treatment of early breast cancer. PhD Thesis, University of London, 2002.
49 Vaidya JS, Wilson AJ, Houghton J, et al. Cosmetic outcome after targeted intraoperative radiotherapy (Targit) for early breast cancer. *Breast Cancer Res Treat* 2003; **82** (suppl 1)**:** 1039.
50 Vaidya JS, Joseph D, Hilaris BS, et al. Targeted intraoperative Radiotherapy for breast cancer: an international Trial. Proceedings of the 21st European Society for Therapeutic Radiology and Oncology, Prague, 2002: **21:** (abstr 135).
51 Intra M, Gatti G, Luini A, et al. Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer. *Arch Surg* 2002; **137:** 737–40.

Clinical picture

Bilateral pulmonary artery tumour emboli from renal carcinoma

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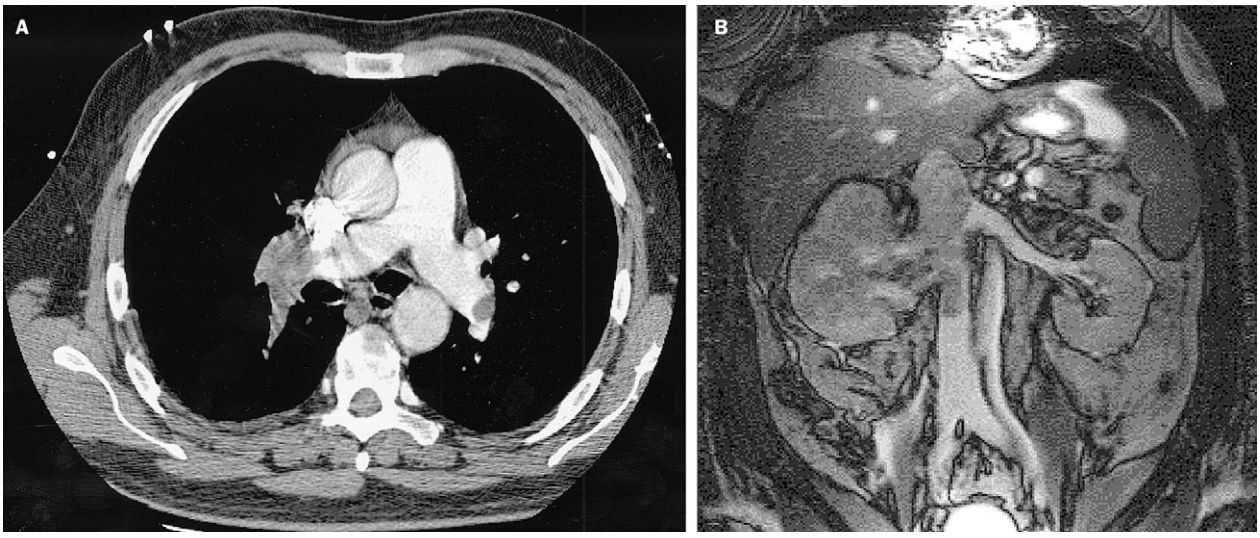

A 53-year-old male presented with shortness of breath and dyspnoea on exertion, which he noticed for several months. CT of the chest showed bilateral main pulmonary artery emboli with extension into the interlobar and segmental arteries, as well as several pulmonary infarcts (figure a). An abdominal 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.

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