

**A NOVEL APPROACH FOR LOCAL TREATMENT OF
BREAST CANCER**

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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AT

UNIVERSITY COLLEGE LONDON

1996-2001

DEDICATED TO

MY FATHER

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Abstract

Early local recurrence of breast cancer most commonly (over 90%) occurs at the site of the primary tumour. This is true whether or not radiotherapy is given and irrespective of the margin status. Whole-organ analysis of mastectomy specimens on the other hand, reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. Therefore, these occult cancer foci may be clinically irrelevant and it may not be necessary to treat the whole breast with radiotherapy. This 6-wks long course of post-operative radiotherapy after breast conserving therapy is not only inconvenient and costly, but may cause many women from geographically remote areas to choose mastectomy. Targeted Intraoperative radiotherapy (TARGIT) to the peri-tumoural area alone might provide adequate local control. 'Intrabeam' (*PeC*) is a portable electron-beam driven device that can deliver therapeutic radiation (soft x-rays) in 20-30 minutes within a standard operating theatre environment. The pliable breast tissue - the target - is wrapped around a spherical applicator - the source - providing truly conformal

radiotherapy. The prescribed dose is 5 & 20Gy at 1cm and 0.2cm respectively, from the tumour bed. The biologically effective dose is 7-53Gy for $\alpha/\beta=10$ and 20-120Gy for $\alpha/\beta=1.5$. In our pilot study of 26 patients (age 30-80 years, T=0.42-4.0cm), we replaced the routine post-operative tumour bed boost with targeted intra-operative radiotherapy. There have been no major complications and no patient has developed local recurrence, although the median follow-up time is short at 34 months. The cosmetic outcome is satisfying to both the patient and the clinician. Having established the feasibility, acceptability and safety in the pilot study, we started in March 2000, a randomised trial that compares TARGIT with conventional post-operative radiotherapy for infiltrating duct carcinomas, with local recurrence and cosmesis as the main outcome measures. Patient accrual in this trial has been excellent and it has attracted several international collaborative groups. If proven effective, TARGIT could eliminate the need for post-operative radiotherapy potentially saving time, money and breasts.

CHAPTER 1

Local treatment of breast cancer and the significance of local recurrence

The shift from radical surgery to conservative surgery

Historical Perspectives

The Edwin Smith Papyrus was written about 1700 BC but is based on writings of the Old Kingdom (2640 BC) -- the time of Imhotep. It describes breast cancer thus...*"If thou examinest a man having bulging tumors on his breast, and if thou puttst thy hand upon his breast upon these tumors, and thou finds them very cool, there being no fever at all when thy hand touches him, they have no granulation, they form no fluid, they do not generate secretions of fluid, and they are bulging to thy hand. Thou should say concerning him: One having bulging tumors. An ailment with which I will not contend"*. It describes eight cases of tumours or ulcers of the breast that were treated by cauterisation, with a tool called "the fire drill." The futility of such treatment was also recognised by the author- "There is no treatment."

Breast cancer, an enigmatic disease with an unpredictable natural history has been a fertile soil for the development of hypothetical models each with their therapeutic consequence. Until the discovery of the cellular nature of

cancer the disease was managed according to Galenic principles, the disease being visualised as an excess of melancholia (black bile) that coagulated within the breast[Porter, 1998] ridding the body of this excess of black bile involved venesection, purgation, cupping, leaching, enemas and bizarre diets (many "alternative" treatments of breast cancer to this day are in fact a form of neo-galenism).

In the mid 19th Century the humoral theory of breast cancer was overturned by a mechanistic model which described the disease as a phenomenon arising locally within the breast and then spreading centrifugally along lymphatics to be arrested in the first echelon of lymph nodes which acted as a barrier to onward spread by their innate filtering capacity. A second echelon of lymph nodes existed like the casement walls of a medieval town protecting the citadel at its centre. Charles Moore, (1821-79) a surgeon from the Middlesex Hospital in London believed that the only way to cure breast cancer was very extensive surgery, in which the tumour was not violated[Moore, 1867]. Samuel Gross (1838-89) [Gross, 1880] agreed with this and emphasised the importance of axillary dissection. The therapeutic consequences of such a

belief was the development of the Halsted radical mastectomy, at the end of the 19th century [Halsted, 1894b;Halsted, 1894a].

The Halstedian Era – focus on local therapy

William Halsted (1852-1922) operated at a time when the triumph of mechanistic principles was at its peak. The common man had begun enjoying the fruits of the industrial revolution. However, on the more fundamental level, it was at this time, that, the limits of Newtonian laws of nature in the physical sciences were being realised by Einstein and Hiensenburgh. Biological and medical sciences, on the other hand, were still considered too different from the physical sciences to be affected by these changes. Naturally, Halsted's 'complete operation' was based on straightforward and logical concepts about tumour biology: that the tumour spreads centrifugally in the breast to the surrounding lymphatics and lymph nodes and thence to the rest of the body. His classical operation included *en bloc* dissection of the breast and surrounding tissue including the lymphatic drainage sites. 'The suspected tissues should be removed in one piece, (1) lest the wound become infected by the division of tissue invaded by the disease or by lymphatic

vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in a piecemeal extirpation'[Halsted, 1894b;Halsted, 1894a]. His surgical expertise was remarkable...`the operation, as we perform it, is literally an almost bloodless one...` and for the first time, breast cancer seemed curable. His recurrence rates (6% local + 14% regional) at 3 years of follow up were very low, compared to the other series at that time (56%-82%). Clearly, he believed that `we are encouraged to hope for a much brighter, if not very bright, future for operations for cancer of the breast` and titled his paper `The results of operations for cure of cancer of the breast`. Halsted's pioneering work in breast cancer served as a model for many other solid cancers and his principles are still successful in cancers such as squamous carcinoma of the head and neck -the commando operation and cervix - the Wertheim's operation.

Fisher's theory of biological pre-determinism - focus on systemic therapy

Unfortunately, only 23% of patients treated by Halsted survived 10 years[Lewis and Rienhoff, 1932]. The first attempted solution to this was surgery that was even more

radical. Internal mammary lymph nodes that receive about 25% of the lymphatic drainage of the breast were not removed in the 'complete operation'. Non-randomised studies indicated that operations that were more radical improved survival[Urban, 1978]. However, in randomised trials, overall, no real benefit could be demonstrated at a five year follow up [Lacour et al., 1976] [Meier et al., 1985]. Although a subsequent subgroup analysis at 10 year follow up [Meier et al., 1989] did suggest a possible benefit in those with medial and central quadrant tumours, this was based on a small number of patients (78 patients) and this effect was not seen in a larger trial with similar follow up which involved 1453 patients[Lacour et al., 1983]. Although the patients who did not receive the extended radical mastectomy had more local recurrences, these occurred mostly in patients who developed distant metastasis and the overall the survival in the two groups was not different. Moreover, even when the tumour seemed to have been completely 'removed with its roots', the patients still developed distant metastases and succumbed: 30% of node-negative and 75% of node positive patients eventually succumbed to breast cancer when they were treated by radical surgery alone[Fisher and Gebhardt,

1978]. Prompted by the failures of radical operations to cure patients of breast cancer, Bernard Fisher[Fisher, 1980] postulated that cancer spreads via blood stream even before its clinical detection and possibly during tumour manipulation during surgery, with the outcome determined by the biology of tumour host interactions. Based on this concept of "biological pre-determinism", he postulated that 1) the extent of local treatment would not affect survival 2) systemic treatment of even seemingly localised tumours would be beneficial and may offer a chance of cure. This was not the first time that the radicality of surgery was questioned. It has been questioned since 1923[Ewing, 1928]. Geoffrey Keynes of St Bartholomew' Hospital believed that wide excision and radiotherapy would have the same survival as mastectomy[Keynes, 1937;Keynes, 1952]. However, it was only in the early 1960s that several pioneers in the field set up randomised clinical trials to test the hypothesis. Indeed the results of these trials testing of the hypothesis that adjuvant systemic treatment should improve survival provide a 'proof of principle'. However, we must realise that the proof is more to the letter than in the spirit. It was expected that the adjuvant systemic therapy would probably be able to 'cure' the patients who had

'micro-metastatic' disease. This is evident from the size of the first ground-breaking trial reported in the New England Journal of medicine in [Bonadonna et al., 1976]. This trial was reported at a follow up only 27 months and with only 386 patients, it had only a 27% power to detect the 25% relative risk reduction, i.e., 6% in their 24% relapse rate. They had 80% power to detect only a 50% reduction in relapse rate- clearly the expectations were much higher than the reality. It was a fortunate play of chance that this trial was positive, otherwise, chemotherapy for breast cancer would have had a premature death. As we now know several subsequent trial results were contradictory and it was only when the 1985 Oxford overview [Early Breast Cancer Trialists' Collaborative Group, 1988] was performed that the truth was evident - that the benefits from systemic therapy are modest - a relative risk reduction of about 25% which is about 8-10% in absolute terms. Although this was a great triumph, we must realise that we have progressed little since the last 15 years. As far as systemic 'cure' of the disease is concerned, the way forward is to develop new models of disease based on non-mechanistic principles such as mathematics of non-linear dynamics and chaos theory, using tools such as neural

networks and to develop novel systemic treatments that are more specific and aimed to tame rather than kill cancer cells. Of course, the utopian wish that an evolution of a new treatment should follow the “proper” route -from philosophical model to laboratory and finally to the bedside- is has only rarely been realised and most advances in use today are a result of either serendipity or innovative new treatments tested in clinical trials. Nevertheless, one cannot stop waiting for the giant leap that a Kuhnian revolution could make.

The rest of this chapter and indeed this thesis concentrates on local control of the disease.

Extent of Local therapy

As regards the extent of local treatment, there have been several randomised trials that have tested less vs. more surgery and the effect of adjuvant radiotherapy. In general these trials also suffered from small numbers and although some individual trials did have significant results on their own, it was necessary to pool the data together in the Oxford overview [Early Breast Cancer Trialists' Collaborative Group, 1995; Early Breast Cancer Trialists' Collaborative

Group, 2000]to make the issues clear. The main issues at stake were:

- 1) Does more extensive surgery improve survival?
- 2) Does addition of radiotherapy to mastectomy improve survival? And can it substitute for less extensive surgery in terms of both local control and survival?

Does more extensive surgery improve survival?

The 1995 Oxford overview[Early Breast Cancer Trialists' Collaborative Group, 1995] of 26000 women from 36 of these trials concluded that more radical local treatment, whether surgery or adjuvant radiotherapy, does not have any influence on appearance of distant disease and overall survival. This is in spite of the increase in local recurrence rates with less radical local treatment, i.e., although post-operative radiotherapy had a substantial effect on reducing local recurrence rates, it did not improve overall survival or distant disease free survival. At the same time, the collateral support for the Fisher's hypothesis came from the fact that although the "early" detection of cancer (before systemic spread) by screening improved mortality, it did so only in women >50 years and the reduction in mortality was very modest – only a 25 % overall relative risk

reduction. Thus, the above data could be taken as powerful corroboration of Fisher's theory that metastases of any importance have already occurred *before* the clinical or radiological detection of at least 75% of breast cancers.

What does radiotherapy add to either conservative surgery or mastectomy?

The questions whether radiotherapy can replace more extensive surgery and whether radiotherapy is needed after mastectomy have been answered to a greater accuracy in the 2000 overview because many more trials results were now available.

The CRC group (the Kings-Cambridge Trial) was the first to point out that there was an excess of non-breast cancer mortality in the group of women who were randomised to receive radiotherapy and had a left-sided breast cancer. They suggested that this could be because of the orthovoltage radiotherapy which had considerably more scatter and would have damaged the coronary vessels [Haybittle et al., 1989; Houghton et al., 1994; Cuzick et al., 1994]. Thus in the CRC trial, although the breast cancer mortality was reduced by radiotherapy, this beneficial effect was completely erased by the harmful effect on the heart, thus showing overall no survival benefit. Other radiotherapy

trials also did not find any improvement in overall survival with radiotherapy (Manchester Christie and Stockholm trials). This finding was borne out in the overview of randomised trials testing the benefit of radiotherapy after mastectomy[Cuzick et al., 1987]

In addition to cardiac deaths, there was increased incidence of second malignancy in those treated with radiotherapy. Ipsilateral but not contralateral lung cancer risk was increased 3 fold[Neugut et al., 1994] and this increased multiplicatively 32 fold among smokers. Risk of squamous carcinoma of oesophagus cancer was also increased-cell carcinoma increased RR 5.42 (95% CI, 2.33 to 10.68) [Ahsan and Neugut, 1998].

The 'accepted wisdom' is shaken?

Thus by mid-1990s there was widespread belief that the extent of local treatment did not affect the long-term outcome. This was probably already determined by the time the cancer was diagnosed. The publication of two large Danish trials has shaken this 'proven' consensus. In these trials, involving women with larger breast tumours and/or many involved lymph nodes, who received adjuvant chemotherapy or tamoxifen [Overgaard et al.,

1997;Overgaard et al., 1999;Ragaz et al., 1997]. Not surprisingly, there was a reduction in local recurrence rates - but there was also an improvement in the overall 10 year-survival rates - (9%[Overgaard et al., 1997] and 10%[Ragaz et al., 1997]). The trials have been criticised because the surgery for these fairly large tumours was inadequate, thus accentuating the benefit by radiotherapy. However, the radiotherapy techniques in these two studies minimised the dose to the heart and included internal mammary chain in the field. These factors could have contributed to the large improvement in survival. Another explanation for this large magnitude of the difference in survival rates could be a statistical quirk. Let us assume that radiotherapy does impart a small survival benefit. When several trials are conducted, the different magnitudes of effects seen are expected to follow normal distribution. A sufficiently large trial would be highly likely to detect this small difference whereas a small trial will rarely yield a positive result because of type II error. The effect in a small trial will need to be larger than the real effect (just by chance) for it to be detected at all, consequently, small trials that are positive will usually be those which reveal a larger than real effect.

A meta-analysis by Tim Whelan attempted to look at a specific group- mainly those who received systemic adjuvant therapy. Their hypothesis was that this is probably the only group in which any secondary spread from recurrent disease might have an impact on survival. They found that overall there is indeed a small reduction in mortality from adjuvant radiotherapy [Whelan et al., 2000]. The evidence to support the belief that adequate local treatment is important not only to reduce local recurrence but also to reduce death from breast cancer, was in fact already available in some early surgical trials.

The initial Guy's trials of conservative surgery were started in the 1960s were the first to refute the Fisher's theory that extent of local treatment would not affect survival. They found that radical surgery imparted a significant survival benefit[Atkins et al., 1972], and this beneficial effect has actually been accentuated after 25 years of follow up[Fentiman, 1998;Fentiman, 2000]. In the first series 374 women (>50yrs) with T1, T2, N0 and N1 tumours were randomized to either Halsted mastectomy or wide excision. Both groups were given 25-27 Gy to the gland fields and the wide excision group received additionally 35-38 Gy to the breast. Hence the wide excision group had no axillary

surgery and subsequent axillary irradiation using what is now regarded as a low dose of radiotherapy. After 25 years, local relapse occurred in 26% of the mastectomy group and 50% of the wide excision group ($\chi^2=21.6$, $P < 0.001$). The breast cancer mortality rate at 25 years was 56% in the mastectomy group and 63% in those treated by wide excision ($\chi^2 = 5.33$, $P = 0.02$). The first analysis of this trial indicated that increased risk of axillary relapse was restricted to (clinically) N1 cases and so a second trial was conducted with entry only for those with clinically negative axillae (N0 series). Of 355 cases entered, 133 were randomized to mastectomy and 122 to wide excision, with the same radiotherapy schedule as was used as in the original series. After 25 years local relapse occurred in 18% of the mastectomy cases and 54% of the wide excision group ($\chi^2 = 30.6$, $P < 0.001$). There were significantly more distant relapse in the latter group ($\chi^2 = 6.32$, $P = 0.01$), and a significant increase in breast cancer deaths (57% versus 44%,; $\chi^2 = 4.27$, $P = 0.04$). These two trials, conducted before the widespread introduction of systemic adjuvant therapy, both indicate the long-term effects of inadequate primary treatment. Inadvertent failure to treat the axilla effectively

led not only to significantly increased axillary relapse rates but also to more deaths from metastatic disease.

In a large study from Denmark, [Axelsson et al., 1992] analysed the records of 13,851 patients registered by the Danish Breast Cancer Cooperative Group (DBCG). They found that node negativity was determined not only by small tumour size, but also by the number of lymph nodes removed. Where 10 or more negative lymph nodes were removed, significantly better axillary recurrence-free survival ($P < 0.0001$), over-all recurrence-free survival ($P < 0.0001$) and survival ($P < 0.005$) were found. To see whether axillary surgery may perhaps be less important they, analysed the records of 4771 patients with tumour diameters ≤ 10 mm [Axelsson et al., 2000]. As expected, they found more axillary metastases in group T1b tumours than in T1a. Mean number of positive nodes was related to number of nodes removed, and again, when 10 or more nodes were removed a significantly lower axillary recurrence rate and better recurrence-free survival were demonstrated. It was not possible to define a patient group where axillary surgery was superfluous. The authors concluded that adequate axillary surgery is necessary for adequate local control.

Another study, albeit non-randomised, also suggested that local control does impact overall survival. This study from Cardiff [Shukla et al., 1999], used prospective long-term follow-up monitoring of two contemporaneous groups of patients, within a single unit, who were treated identically except for the one variable of local treatment policy, i.e., conservative or radical. A total of 451 patients with operable breast cancer were chosen from 567 consecutive patients with breast cancer who were treated between 1970 and 1979 in the University Department of Surgery. Two hundred forty-one patients were treated using a conservative approach and 210 were treated using a radical approach. At 132 months, the survival rate (58% vs. 42%) and median survival time (> 132 vs. 100 months) were significantly improved for the radically treated group ($P < .01$). The treatment groups were comparable in terms of age, menopausal status, tumour size, histologic grading, and Nottingham Prognostic Index values and the advantage of the radical policy persisted when examined in relation to each of these prognostic factors. This was related to a reduced loco-regional recurrence rate and provided evidence that local therapy influences long-term outcomes for patients with breast cancer.

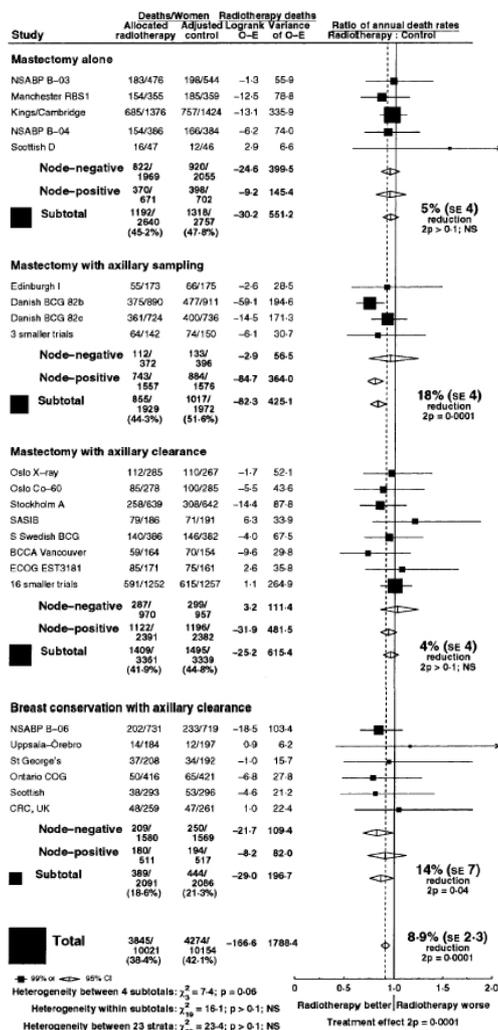
The latest Oxford Overview

The speculation about a small potential survival benefit from radiotherapy has been borne out in the latest world overview. The Oxford Group has repeated the meta-analysis of randomised trials testing the value of radiotherapy. They used individual patient data and included 40 published and unpublished trials [Early Breast Cancer Trialists' Collaborative Group, 2000] with special attention to the Danish trials. This meta-analysis (see figure) showed that radiotherapy reduced the local recurrence from 27.2% to 8.8% at 10 years. Breast cancer mortality was indeed reduced ($2p=0.0001$) but other mortality was increased ($2p=0.0003$). Thus, there was no statistically significant difference in survival. The main hazard of radiotherapy was vascular (RR 1.3) which was the only cause separately statistically significant. In addition, mortality from respiratory and second neoplasms was also increased. Overall, the 20-year survival was 37.1% with radiotherapy versus 35.9% control ($2p=0.06$), and 10-year survival was 56.6% vs. 54.5%, respectively. After the first 2 years, the annual death rate among patients allocated to radiotherapy was about 21% higher. If the harmful effects of adjuvant radiotherapy could be completely avoided,

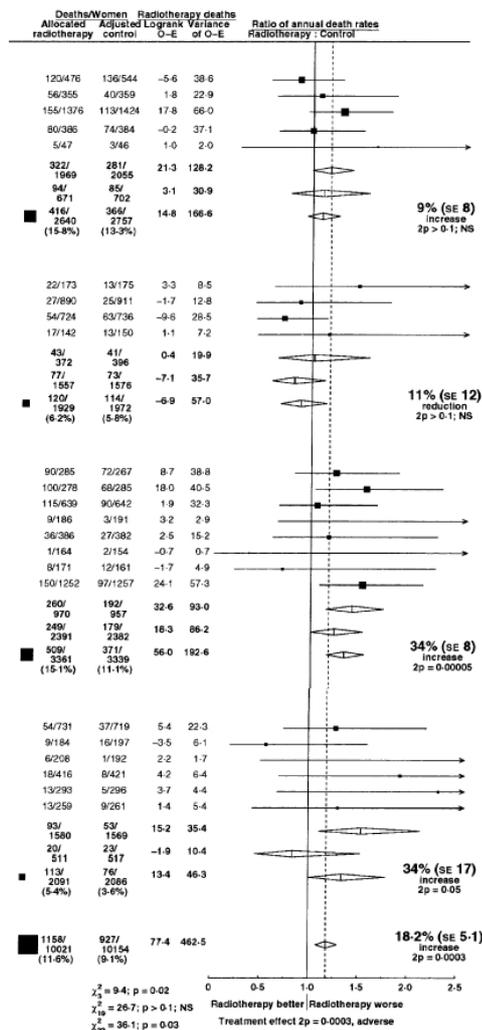
possibly by using modern radiotherapy techniques, it would be expected to produce an absolute increase in 20-year survival of about 2-4% (except for women at particularly low risk of local recurrence). The average hazard seen in these trials would, however, reduce this 20-year survival benefit in young women and reverse it in older women. Radiotherapy in general reduced the relative risk of local recurrence by two thirds (66% relative risk reduction= e.g. from 30% to 10% i.e., a 20% absolute risk reduction) and reduced the risk of breast cancer death by about a fifth of that reduction (i.e., $66/5 = 13.5\%$ relative risk reduction = e.g. $20/5 = 4\%$ absolute risk reduction). Thus, the magnitude of the beneficial effect of radiotherapy is small and if radiotherapy side effects can be completely avoided, it could improve the 20 year survival by about 2-4% the benefit mainly limited to those women who have a high risk of local recurrence.

These latest results have shown that survival benefit from adequate local treatment is small, but real and since it can become apparent only after long term follow up, it can be missed. Of note, this small benefit is equivalent in magnitude to that obtained by adjuvant systemic chemotherapy in those above 50 years of age!

Breast cancer deaths only



Non-breast-cancer deaths



Local recurrence after breast conserving therapy

Local recurrence of breast cancer is a very emotionally laden subject and is associated with a sense of failure for both the patient and the doctor. There are several separate issues to consider here:

- 1) Is local recurrence a failure of local therapy only and can be salvaged/ prevented by more aggressive local therapy, or is it a more sinister harbinger of outcome – i.e., is the determinant or expression of a poor prognosis?
- 2) Is margin status important for local control of disease?
- 3) Is multicentricity an important source of recurrence of breast cancer?
- 4) Is it possible that local recurrence is an expression of a field defect in the index quadrant?

Does local recurrence harbinger poor prognosis? If so, is it only a marker or a determinant?

On one hand, local recurrence could be an expression of metastatic disease or a source of tertiary spread. The evidence from randomised studies indicates that although local recurrence is a harbinger of poor prognosis, it is probably not the cause or determinant of it. Thus, local recurrence is only an *indicator* of poor prognosis but not its *determinant*. This is true in the setting of both after

mastectomy as well as breast conserving therapy- as evidence from these trials clearly demonstrates.

The CRC trial

In a trial involving 35 clinicians in the UK, 585 patients were randomised to either receive radiotherapy or not. Radiotherapy reduced the risk of local recurrence significantly (RR 0.43; 95% CI 0.29- 0.63) but there was no overall difference in survival.

The NSABP-B06 trial

In this trial, patients were randomised to receive either lumpectomy only, lumpectomy + radiotherapy or total mastectomy + axillary clearance. Radiotherapy reduced the risk of local recurrence from as much as 35% in those who received lumpectomy only, compared to 10% in those who received lumpectomy + radiotherapy but the survival of this whole group receiving lumpectomy only was not in any way less than those receiving radiotherapy after lumpectomy. Overall, there was no difference in the survival of all these groups. But, after adjustment for fixed co-variables such as tumour size and nodal status, ipsilateral breast tumour recurrence (IBTR) is a powerful independent predictor of

distant metastasis. The patients who developed an IBTR had a 3.14 times the risk of distant disease. However, it is emphasised by Fisher that 'this is only a marker of risk for, and not a cause of, distant metastases. Thus, whole breast radiotherapy or mastectomy only prevent the expression of the marker of high risk but do not actually lower the risk of distant disease. [Fisher et al., 1991a;Fisher et al., 1992;Fisher, 1980] [Fisher, 1980;Fisher et al., 1995]

The two European trials- EORTC trial 10801 and DBCG trial 82-TM

A combined analysis of these trials has recently been published. A total of 1,807 patients with stage I and II breast cancer were randomised to receive Modified Radical Mastectomy (MRM) or Breast Conserving Therapy (BCT). When all patients with a local recurrence in these trials were analysed, the survival rates were 58% and 59% for MRM and BCT respectively and the actuarial survival curves and the actuarial loco-regional control curves were similar. The type of primary local treatment (MRM or BCT) did not have any prognostic impact. The overall survival after MRM or BCT was similar in these two European randomised trials. This further reinforced the concept that early local

recurrence is an indicator of a biologically aggressive tumour; early loco-regional relapse carries a poor prognosis and salvage treatment only cures a limited number of patients, whether treated by MRM or BCT originally [van Tienhoven et al., 1999].

The proportion of patients who develop distant metastases within 10 years of developing local recurrence is reported to be from 64 % to 85%. Wilner and colleagues report that [Willner et al., 1997], although the prognosis after local recurrence was poor in general (42% overall), there did exist a subgroup with relatively better prognosis: patients with a single chest wall or axillary recurrent nodule (in a patient aged > 50 years), a disease-free interval of > or = 1 year, pT1-2N0 primary tumour, and without tumour necrosis, and whose recurrence is locally controlled. This subgroup of 12 patients (out of a total of 145) had 5- and 10-year survival rates of 100% and 69%, respectively. One may say that this could only be a result of serious data dredging, however, there are supportive data from the Guy's Hospital [Fentiman et al., 1985]. In this study 73 patients who presented with local skin recurrence, but with no evidence of distant dissemination, after a radical mastectomy. They found that only 10 per cent of those with

multiple lesions survived 5 years, and none was alive at 10 years, whereas 42 per cent of those with single lesions survived 5 years and 22 per cent were alive and well at 10 years' post recurrence. The authors emphasise the importance of adequate local treatment of a single skin nodules. These data suggest local relapse is not necessarily a harbinger of poor prognosis in a small subset of patients.

The NSABP-04 trial

In this trial, 1665 women were randomised into three groups a) women treated with either total mastectomy only b) Total mastectomy + radiotherapy and c) Radical mastectomy. There was no difference in survival rates of these three groups despite the fact that in the Total mastectomy group almost 40% of patients would have had positive lymph nodes that would be a potential source of distant spread [Fisher et al., 1981]. This study has been criticised [Harris and Osteen, 1985] on the grounds that the total mastectomy 'only' group did in fact have several nodes excised and this alone could have reduced the difference compared with the group that received either formal axillary surgery or axillary radiotherapy.

The Oxford Overview

In this overview [Early Breast Cancer Trialists' Collaborative Group, 2000] it was clearly found that the local recurrence after wide local excision and axillary clearance was substantially reduced from 22% to 7.2% by radiotherapy ($2p < 0.00001$). Radiotherapy also reduced breast cancer mortality by 14% but increased non-breast cancer mortality by 34%. In absolute terms, this was a reduction in breast cancer mortality from 21.3% to 18.6% (difference = 2.7%) and increase in non-breast cancer mortality from 3.6 to 5.4% (difference = 1.8%). Thus, the overall mortality was not changed by radiotherapy (24% vs. 24.9%, $2p > 0.1$).

Discussion

From all these trials, it appears that local recurrence, cannot, in general be a source of tertiary spread in more than say 5% of cases – because if it were, then we would have expected that the group which did not receive any radiotherapy and experienced three times the local recurrence as the group which received radiotherapy, would have fared much worse in terms of overall survival. This however, was not the case. Those who did not develop local recurrence because they received radiotherapy were simply

prevented (by radiotherapy) from expressing their poor prognosis locally, which was expressed systemically; thus overall survival was equal in the two arms.

Is margin status important for local control of disease?

Whether a positive margin is a marker of a high risk of local recurrence or a cause of it –can only be ascertained by a clinical trial in which patients with positive margins are randomised to either receive further surgical excision before radiotherapy, or have only the routine radiotherapy. Such a trial has not yet been performed. However, several surrogate findings can give us some clues. The answer seems to be similar to that for local recurrence- just as local recurrence is only a marker for distant disease, a positive margin appears to be a marker for a disease that is likely to behave aggressively- locally recurrent and with poor long term prognosis. One study from the Royal Marsden Hospital found that positive margins did not have any bearing on local recurrence [Assersohn et al., 1999]

Randomised studies

A subgroup analysis was performed by the CRC group [Potyka et al., 1999] to explore the importance of positive margins after wide local excision of invasive cancers. Although the group of patients with positive margins were at a higher risk of suffering local recurrence, the proportional reduction of this risk by radiotherapy in this group was equal to that for those with negative margins. If positive margins were the cause of local recurrence, we would have expected radiotherapy to have a much larger effect on the group with positive margins compared to the group with negative margins. In actual fact, it was found that radiotherapy reduces the risk of local recurrence whether or not margins are positive.

For DCIS however, it appears that in addition to absence of radiotherapy, young age, symptomatic detection of DCIS, and growth pattern, involved margin is an important predictor of local recurrence[Bijker et al., 2001], although one cannot be certain that it is indeed the determinant.

Non randomised series

In case of DCIS, Nigel Bundred's group [Chan et al., 2001] and Mel Silverstein's group have found that positive

margins are associated with increased risk of local recurrence and that addition of radiotherapy did not fully compensate for 'inadequate' surgery. However Mel Silverstein found that if the margin of excision was more than 1mm then radiotherapy did not make much statistically significant difference in the local recurrence rate that was already very low [Silverstein et al., 1999]. However, these findings in DCIS appear to be different from those in invasive carcinoma.

Obedian and Haffty have presented a retrospective analysis [Obedian and Haffty, 2000] of 871 patients (treated between 1970-90) of whom 294 had re-excision. For this analysis, patients were divided into four groups based on final pathologic margin status: negative (n = 278), close (typically within 2 mm, n = 47), positive (n = 55), or indeterminate (n = 491). Breast relapse-free survival at 10 years was 98% for patients with negative margins versus 98% for those with close margins versus 83% for those with positive margins versus 82% for those with indeterminate margins. It is noteworthy, firstly, that more than half of these patients had indeterminate margins- not all of which could be considered to have positive margins. In addition, patients with negative margins were more likely

than those with positive margins to have T1 mammographically detected lesions, to have negative nodal status, and to have undergone re-excision. Patients with positive margins were more likely to receive adjuvant chemotherapy or hormone therapy ($P = 0.001$). The authors themselves state that although the negative margin status conferred an overall survival and distant metastasis-free survival advantage, this difference is confounded by the earlier stage of disease in these patients; not surprisingly, margin status did not influence overall survival in multivariate analysis.

In a German study of 1036 evaluable patients, [Rauschecker et al., 1998] with a median follow-up of 97 months, 237 events (local recurrence, regional recurrence, distant metastases, contralateral breast cancer or death of the patient without previous recurrence) occurred. The local recurrence rate of the whole patient population was 8.8% at 8 years. Out of all prognostic factors examined, only tumour size and grade had a significant influence on recurrent disease. Although, event-free survival decreased in cases with 'uncertain' tumour margins, the width of the margin has no influence on disease recurrence.

Park and colleagues [Park et al., 2000] studied in 533 patients, the relationship between pathologic margin status and outcome at 8 years after breast-conserving surgery and radiation therapy. Each margin was scored (according to the presence of invasive or in situ disease that touched the inked surgical margin) as one of the following: negative, close, focally positive, or extensively positive. The patients with close margins and those with negative margins both had a local recurrence rate of 7%, those patients with extensively positive margins had an LR rate of 27%, whereas patients with focally positive margins had an intermediate rate of LR of 14% - which was reduced to 7% if they had received adjuvant systemic therapy. In a multiple logistic regression model, pathologic margin status and the use of adjuvant systemic therapy were the most important factors associated with LR among patients treated with breast-conserving surgery and radiation therapy.

Moore and colleagues [Moore et al., 2000] found that lobular cancers had a high incidence of positive margins (51%). However, in randomised trials, many of which included those that did not routinely evaluate margin status, lobular cancers did not behave differently from the

usual invasive ductal cancers after breast conservative surgery. However, in another study, with similar main results, [Mai et al., 2000] the high risk of positive margins for ILC was limited to those that were greater than 2cm in size and moderate or high nuclear grade.

In the analysis within one randomised trial of adjuvant or neo-adjuvant systemic therapy, it was found that among 184 patients, 38% had a positive margin [Assersohn et al., 1999] and had not received any further local surgery. However, the local recurrence rate and survival was not in any way different in this group.

Freedman and colleagues studied the association between a positive resection margin and the risk of ipsilateral breast tumour recurrence (IBTR) after conservative surgery and radiation. In a series of 1,262 patients with clinical Stage I or II breast cancer were treated by breast-conserving surgery, axillary node dissection, and radiation between March 1979 and December 1992. Forty-one percent had a single excision, and 59% had a re-excision. The final margins were negative in 77%, positive in 12%, and close (< or = 2 mm) in 11%. Chemotherapy +/- tamoxifen was used in 28%, tamoxifen alone in 20%, and no adjuvant systemic therapy in 52%. At 10 years, a significant

difference in IBTR became apparent (negative 7%, positive 12%, close 14%, $p = 0.04$). The highest risk was observed in patients with persistently positive (13%) or close (21%) ($p = 0.02$) margins. IBTR was delayed in patients who received adjuvant systemic therapy but this delay to IBTR was seen mainly in patients with close or positive margins, with little impact on the time to failure in patients with negative margins. At 5-years the cumulative incidence of IBTR in patients with close or positive margins was 1% with adjuvant systemic therapy and 13% with no adjuvant therapy. However, by 10 years, the CI of IBTR was similar (18% vs. 14%) due to more late failures in the patients who received adjuvant systemic therapy. Thus, a close or positive margin is associated with an increased risk of IBTR even in patients who are EIC-negative or receiving higher boost doses of radiation, which was reduced by systemic therapy.

The concept of margin is in itself ambiguous. As will be discussed in the next chapter, many small cancers in addition to the primary tumour in about are present in 2/3rds of breast specimens. Thus, any one of these occult cancers could be present at the 'margin' of excision of the dominant tumour, irrespective of how widely it was excised.

As has been seen in many of these studies, it is the grossly or diffusely involved margin that is probably indicative of significant and residual disease that could give rise to local recurrence, rather than the focally involved margin which many times might represent only incidental 'biopsy' of a multicentric focus in the breast.

Does local recurrence occur because of a Field defect?

The morphologically normal cells surrounding breast cancer demonstrate a loss of heterozygosity, which frequently is identical to that of the primary tumour [Deng et al., 1996]. So these 'normal' cells are already on the brink of becoming cancer.

Aromatase activity in the index quadrant is higher than other quadrants [O'Neill et al., 1988] and via oestrogen it can stimulate mutagenesis, growth and angiogenesis [Lu et al., 1996]

In the NSABP-B06 trial [Fisher et al., 1992], all the local recurrence in the no-Radiotherapy arm occurred in the index quadrant again suggesting that it is probably a field defect.

Several studies have investigated whether young age was a risk factor for local recurrence after breast conserving therapy and whether radiotherapy had a differential effect according to age. Patients with ipsilateral breast tumour recurrence (IBTR) have an increased risk of carrying mutant p53 gene (23% vs. 1%)[Turner et al., 1999b;Turner et al., 1999a]. In addition, young patients (<40 years) with IBTR have a disproportionately increased risk (40%) of carrying a deleterious BRCA1/2 gene mutation[Turner et al., 1999b]. This suggests that such local recurrence is probably related more to the background genetic instability rather than a different tumour biology at younger age.

Is multicentricity an important source of recurrence of breast cancer? - the site of local recurrence

A striking fact about local recurrence after conservative therapy with or without radiotherapy is that it almost always occurs in the same area as the primary tumour. In large series of breast conservation studies, it has been seen that >90% of early breast recurrences occur in the quadrant that harboured the primary tumour ([Harris et al., 1981], [Clark et al., 1982], [Schnitt et al., 1984], [Clarke

et al., 1985], [Kurtz et al., 1989b], [Boyages et al., 1990], [Fowble et al., 1990], [Fisher et al., 1992], [Clark et al., 1992], [Veronesi et al., 1993]).

Study	No. of patients	Proportion of recurrences in the index quadrant
Clark RM, 1982	680	96%
Schnidt SJ, 1984	231	83%
Boyages J, 1990	783	81%
Kurtz, JM, 1990	1593	86%
Fisher B, 1992 (RT)	488	100%
Veronesi U, 1993	570	90%
Clark 1992 (RT arm)	416	(19/23) 83%
Clark 1992 (no RT arm)	421	(103/108) 86%
TOTAL	5182	91%

It is important to recognise that this is true whether or not radiotherapy is given [Clark et al., 1992]). That means that whatever that is the cause of local recurrence – its location remains in the index quadrant and is not affected by radiotherapy. Secondly, we also know that local recurrence occurs in the index quadrant irrespective of clear margins. Of the breast conserving trials that have tested the effect of radiotherapy, the NSABP-B06, [Fisher et al., 1985] [Fisher, 1980;Fisher et al., 1996] Ontario[Clark et al., 1992;Clark et al., 1996], Swedish[Liljegren et al., 1999] and Scottish[Forrest et al., 1996] trials had less extensive

surgery compared with the Milan III trial[Veronesi et al., 1993]. The recurrence rate in the Milan III trial was low (8.8% vs. 24-27% in other trials) even in the control group albeit at the cost of cosmesis. Nevertheless, radiotherapy reduced it even further and at the same proportional rate as in other trials. If local recurrence was caused by residual disease, then radiotherapy should have affected much larger proportional reduction in those patients with positive margins or less extensive surgery. However, radiotherapy also reduces the rate of local recurrence in those patients with negative margins, which further suggests that it does not arise from overlooked foci of DCIS. We propose that the recurrence could arise a) from circulating metastatic cancer cells lodging in the highly vascular surgical bed rich in cytokines e.g., IGF I, VEGF (local relapse does harbingers a poorer prognosis) or b) genetic instability of morphologically normal cells adjacent to the tumour. Thus although the margins of excision are morphologically clear they may be genetically unstable. In fact, loss of heterozygosity has been already found in morphologically normal breast tissue around breast cancer.[Deng et al., 1996]. In addition, the milieu in the index quadrant is probably congenial to mutagenesis – aromatase activity in

the index quadrant is higher than other quadrants [O'Neill et al., 1988] and via oestrogen it can stimulate mutagenesis, growth and angiogenesis [Nakamura et al., 1996].

CHAPTER 2

Multicentricity of breast cancer: Whole organ analysis and clinical implications

Introduction

William Halsted's paradigm of systematic centrifugal spread of breast cancer was the prevalent consensus for nearly 50 years. However, the fact that many of his patients, even when nodes were not involved died from breast cancer, in spite of having had a 'curative operation to remove the tumour from its roots', led many researchers, Bernard Fisher in particular, to seek alternative theories to explain the natural history of breast cancer, and suggest that less mutilating operations might have similar outcomes especially in terms of survival. In the mid-20th century, the science of randomised clinical trials was developing fast and people started contemplating testing the hypothesis that less radical surgery would have equivalent survival outcome to the more radical approach.

Around the time when the conservative breast surgery was being tested in clinical trials, many studies tried to explore the reasons for recurrence of breast cancer. Several autopsy studies since the 1970s revealed that multiple occult cancers were not uncommon in thyroid and in the prostates of elderly men. A remarkable autopsy study from Denmark[Nielsen et al., 1987] was reported in 1987. These

investigators studied 110 women who had died of medico-legal causes. They simulated a bilateral modified radical mastectomy and then studied the specimens exhaustively. The whole breast was sectioned and examined. They studied some 60,000 paraffin blocks. The median age of these women who had mostly died of accidental causes was 39 years. Even then 20% of the breast specimens revealed microscopic breast carcinoma. This was mostly *in situ* carcinoma but 10% of these were invasive cancers. The proportion of women rose to 1/3rd in the above 50 age group. Clearly, most of these occult cancers would not have surfaced in these women's lifetimes. From population studies, it can be estimated that more than only about a quarter of these occult lesions would go on to become clinically overt cancers.

Many studies have investigated the multicentric nature of breast cancer in mastectomy specimens ([Qualheim and Gall, 1957],[Gallager HS and Martin, 1969], [Hutter and Dim, 1971], [Shah et al., 1973], [Rosen et al., 1975], [Lagios, 1977], [Westman-Naeser et al., 1981], [Sarnelli and Squartini, 1986], [Spinelli et al., 1992], [Anastassiades et al., 1993]). Although some of these studies ([Gallager HS and Martin, 1969], [Hutter and Dim, 1971], [Lagios,

1977]) used radiography, it was Egan ([Egan et al., 1969], [Egan, 1982]) who standardised the “correlated pathological-radiological” method of whole organ analysis which provides optimum sampling of breast tissue. The incidence of multicentricity found in these studies have varied from 18%, when 1-2 random samples from each quadrant are examined ([Spinelli et al., 1992]), to 69% when 5mm sections of whole breast are examined using the Egan’s method ([Egan, 1982]). The principal aim of all these studies has been to find the incidence of multicentric foci (MCF) in the breast. Holland et al.[Holland et al., 1985]in their landmark paper addressed the additional issue of distribution of MCF in terms of their distances from the primary tumour. They showed that MCF were within 2 cm of the tumour edge in 53% patients and within 4cm in 90% of patients. The findings expressed in this manner gave an impression that most MCF are present close to the tumour.

We studied the spatial relationship within the breast of multicentric foci (MCF) with respect to the primary tumour in 30 patients using the Egan’s technique. We used two new approaches to this problem and investigated the spatial distribution not only in one dimension in terms of distances

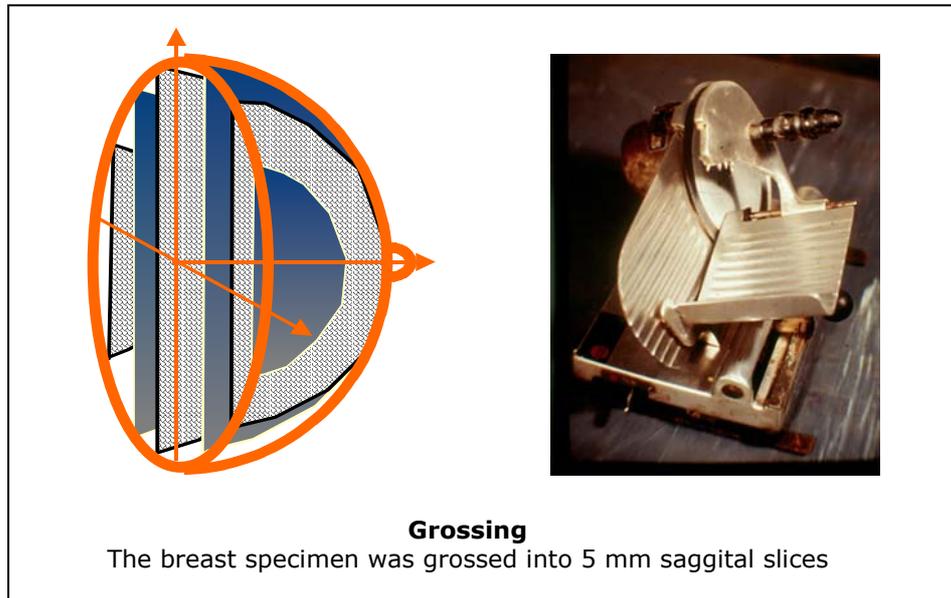
from the primary tumour, but also in two- and three-dimensional analysis within the respective breast specimen, viz., 1) We plotted the relative distribution of MCF and the primary tumour within the 4 breast quadrants and 2) we calculated the volume of breast tissue that would be required to be surgically excised, expressed as a percent of the total breast volume, to include all MCF in each breast. Since we analysed the spatial distribution of all lesions, we chose not to differentiate between multicentric and multifocal lesions[Holland et al., 1990].

Method

Thirty modified radical mastectomy specimens were studied. All patients had their diagnosis established by fine needle aspiration cytology with the primary tumour in situ. The patients had opted for modified radical mastectomy after all available surgical options including conservative surgery had been explained to them. The specimens were studied using the Egan's correlated pathologic-radiological method which involves freezing, slicing, radiography, grossing and microscopy ([Egan et al., 1969], [Egan, 1982]). The superior and lateral margins of the breast specimen and the 6'o clock position were marked with ink.

Axillary tissue was excised and processed separately for dissection of axillary lymph nodes, so that the patient's definitive treatment was not delayed. The breast specimen was placed in a tray, covered with silver foil and kept in a -80°C freezer for 4-24 hours. A transverse line across the nipple was marked to indicate the plane of x-axis.

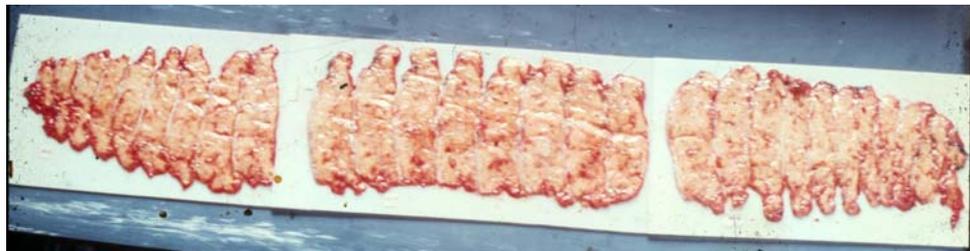
The breast was sliced using a ham slicer. 5mm thick slices were cut in saggital plane starting from the medial side. The slices were laid on acrylic sheets and were radiographed with a mammography machine (100 mA and 22 kV) using high quality mammography plates. The



radiologist examined the mammograms and marked any suspicious areas.



Breast slices and mammogram of slices
(not the same patient)

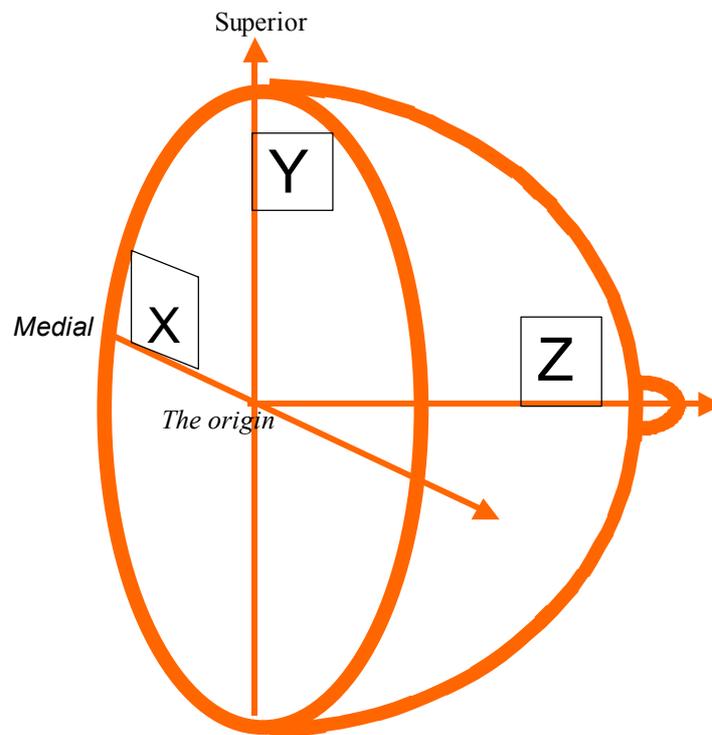


5mm slices of a mastectomy specimen

Gross examination of the slices was then carried out. In every slice, areas that looked or felt suspicious to palpation, and those marked on radiographs, were excised. These suspicious areas were fixed in formalin, embedded in paraffin and studied microscopically. The following lesions were considered as significant: a focus showing ductal

hyperplasia with atypia (ADH), ductal carcinoma in situ (DCIS), infiltrating duct carcinoma (IDC), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) and infiltrating lobular carcinoma (ILC). The analysis for spatial distribution as described below was repeated after exclusion of ADH, ALH and LCIS.

For orientation in space, the point on the base of the breast directly below the nipple was considered the origin of the

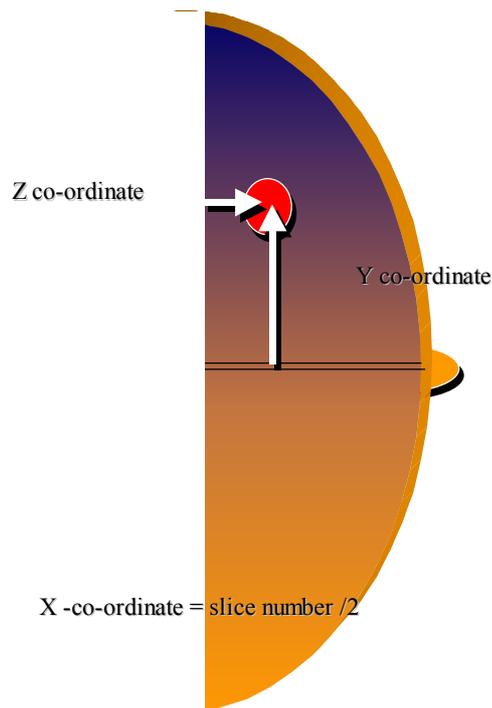


Orientation in Space

Breast was considered to be a hemisphere and the point on the base of the breast immediately deep to the nipple was considered the origin. X-axis was in the medial to lateral direction, y-axis from inferior to superior direction and z-axis from the base to nipple.

frame of reference. The horizontal line from medial to lateral side across the nipple projection was called x-axis;

the vertical line from inferior to superior edge across the nipple-projection was called y-axis; and the line from the origin to nipple was called z-axis. All measurements were made in centimetres. The slice through nipple was



Orientation in space

Determination of co-ordinates on each slice

numbered 0; the medial slices were numbered -1, -2, -3... and the lateral slices +1, +2, +3... .

The x-, y- and z co-ordinates of centre of each suspicious MCF were then measured. Since each slice was 0.5 cm thick, the slice number divided by 2 was equal to the x co-ordinate in cm. The y and z co-ordinates were measured on each slice. The radius of the tumour and all the 3 co-

ordinates of the tumour centre were also measured. These co-ordinates indicated the position within the breast of MCF and the primary tumour. We then calculated 1) distances of MCF from the tumour edge, 2) the relative distribution of primary tumour and MCF in the 4 quadrants of the breast, and, 3) percent breast volume that would be required to be excised to include all MCF. The Microsoft Excel Ver. 5.0 computer programme was used for the above calculations. We wish to point out that the last two methods of analysis are novel and not attempted by previous investigators.

The following calculations were made:

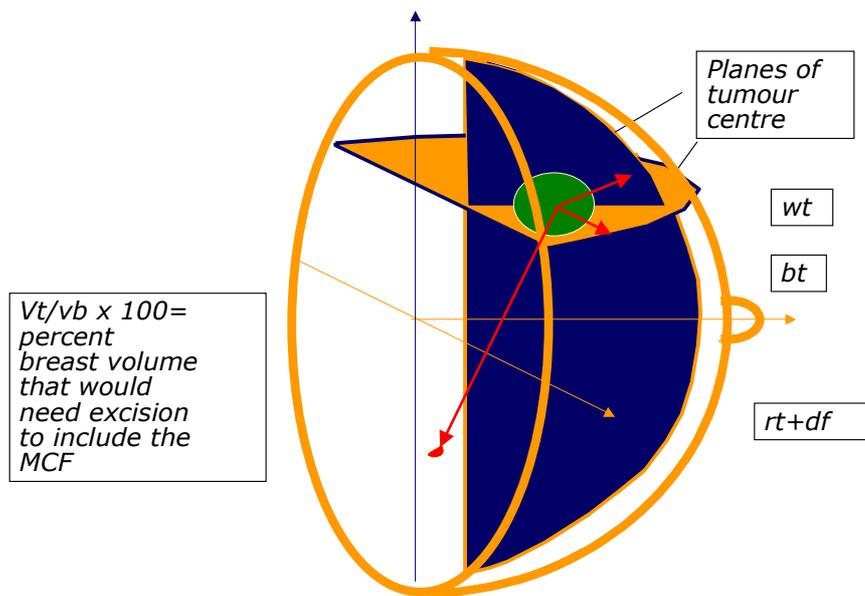
1) Distance of each MCF from edge of tumour was calculated using the formula:

$$df = \sqrt{(xf-xt)^2 + (yf-yt)^2 + (zf-zt)^2} - r_t$$

(df = Distance of each MCF from the edge of the tumour, xf, yf, zf = the co-ordinates of the MCF, xt, yt, zt = the co-ordinates of tumour centre and rt = the radius of the tumour)

2) The relative distribution of the MCF and primary tumour in the four quadrants of the breast were calculated and plotted in two dimensions using the x and y co-ordinates.

3) For each case, the total breast volume (V_b) and the volume of breast tissue that would be required to be excised so that all MCF are included (V_t) was calculated. We expressed the latter as percent of total breast volume.



Volume calculations: Once the co-ordinates of each MCF and each tumour was known, the proportional volume of breast tissue that would be required to

The following formulae were used for this calculation:

Total volume of breast	$V_b = \frac{2}{3} \times \Pi \times h/2 \times b/2 \times w$
Breast volume that would be required to be excised to include the farthest MCF	$V_t = \frac{4}{3} \times \Pi \times (rt + df) \times (ht) \times (bt)$
The percentage of breast volume that would be required to be excised to include all MCF	$=V_t / V_b \times 100$

[h= Vertical height, b= Horizontal width and w= Depth of the breast at nipple, ht and bt = the height and breadth of the breast at the site of the tumour or (rt + df) whichever is smaller]

Statistical analysis was done using Chi-square test and standard tests for correlation and regression.

Most mastectomies, all the pathological specimen handling, its design and actual performance (except microscopy), data collection and analysis was performed by the author.

Results

The patients' ages ranged from 28 to 72 years (mean 49 years). 20 patients were post-menopausal and 10 were pre-menopausal. The mean breast dimensions were: height: 15cm (range 9.5 - 18.5cm), breadth: 13cm (range 10 - 17cm) and depth: 4.5cm (range 3 - 5.5cm). Mean tumour size was 2.98cm (range 1.5 - 5cm). Mean breast volume was 458cc (range 164 - 747cc). We calculated that if the tumours were excised with a 0.5 cm margin, the excised tissue would constitute on an average 9% of the total breast volume. This suggested that, on average, the patients included in the study would have been suitable for

conservative surgery, although that was not the entry criteria for the study and in fact, 3 patients' tumours were 4cm diameter and one was 5cm diameter; these would not have been suitable for breast conserving surgery.

A total of 667 blocks were prepared from the 30 breast specimens. Nineteen breasts were found to harbour MCF. A total of 54 multicentric foci (MCF) were detected. There were 21 foci of hyperplasia without atypia, which were not included for analysis. Of the 54 MCF, 18 (33%) were detected by radiography, and 28 (52%) were detected by gross inspection and palpation and 8 (15%) by both.

Of the 30 primary tumours, 27 were infiltrating duct carcinomas (IDC) and 3 were infiltrating lobular carcinomas (ILC). Of the 54 MCF, 4 were ADH, 16 were DCIS, 17 were IDC, 11 were LCIS and 6 were ILC. There were no foci showing ALH. Of 36 MCF with IDC as primary, 35 were ductal in origin and 1 was ILC. Of 18 MCF with ILC as primary, 16 were lobular in origin and 2 were ADH. The most malignant histological type of MCF in each breast is given in the Table 1. The histological type of MCF (whether infiltrating or in-situ) was not related to its distance from the edge of primary tumour nor to the percent volume of

breast tissue that would be required to be excised to include the MCF.

Table 1: The Most adverse histological type of MCF in Infiltrating duct and in infiltrating lobular carcinomas

Primary tumour	The most adverse histological type of MCF				
	IDC	ILC	DCIS	LCIS	Nil
IDC (27)	9	1	6	-	11
ILC (3)	-	2	-	1	-

IDC= Infiltrating Duct Carcinoma, ILC= Infiltrating Lobular Carcinoma, DCIS= Ductal carcinoma in situ, LCIS= Lobular carcinoma in situ, MCF=Multicentric focus

We investigated whether MCF were generated by lymphatic embolization from the primary tumour. Lymphatic emboli were present within the primary tumour in 3 of the 27 primary IDCs. However, only 1 out of these 3 breast specimens harboured an MCF, and this too was a focus of DCIS. On the other hand, none of the 9 specimens that had IDC as MCF had lymphatic emboli in the primary tumour, suggesting that MCF were not emboli from the primary tumour but rather were independent malignant foci. In

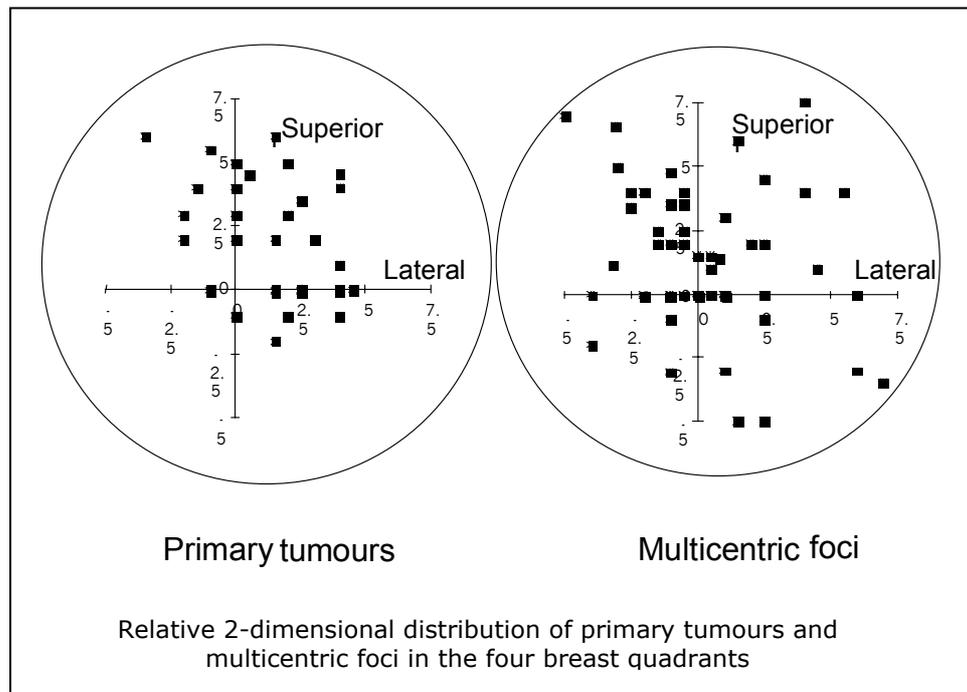
addition, in our analysis of spatial distribution in three dimensions as given below, we did not find any evidence of communications between the primary tumour and MCF.

Distance calculation: We found that 53% of patients had all MCF within 2cm; 67% within 3cm, 80% of within 4cm and 90% within 5cm. Thus, MCF would be left behind in 47% of the patients if the primary tumour were to be excised with a 2cm margin; in 33% with a 3cm margin and in 20% with a 4cm margin and 10% with a 5cm margin. These findings are similar to those observed by Holland et al, 1985 (Table 2).

Table 2: Percent patients in whom MCF would be left behind with increasing excision margin of primary tumour

Excision margin of primary tumour	% patients in whom MCF would be left behind	
	Holland et al, 1985	Present series
2 cm	42%	47%
3 cm	17%	33%
4 cm	10%	20%
5cm	-	10%

Relative Distribution of MCF and Primary tumour: On calculating the relative distribution of MCF and primary tumour within the 4 quadrants of the breast, we found that



while the primary tumour was most common in the upper outer quadrant, MCF were widely distributed in all the 4 quadrants of the breast.

When considered in terms of conventional quadrants, out of the 19 cases that harboured MCF, 14 had MCF outside the index quadrant (a 90° sector of breast which had the primary tumour in its centre).

The distribution of the primary tumour and MCF in the 4 quadrants was statistically significantly different (Chi sq. =8.65, p =0.034) (Table 3).

Table 3: Relative Distribution of primary tumour and MCF in breast quadrants

Quadrant	Primary tumour	MCF
Upper outer	14	13
Upper inner	5	16
Lower outer	10	14
Lower inner	1	11

The distribution of primary tumour and MCF in the 4 breast quadrants of the breast was significantly different. Chi-square = 8.65 $p=0.034$.

Volume calculation: We calculated the proportion of patients in whom MCF would be left behind with increasing volume of breast tissue excised with the tumour (expressed as percent of total breast volume). When all patients were considered, 18/30 (60%) had MCF beyond 10% of the breast volume, 15/30 (50%) had MCF beyond 25% of the breast volume (a quadrant), and 7/30 (23%) had MCF beyond 50% of total breast volume (Table 4).

Table 4: Percent patients in whom MCF would be left behind with increasing volume of breast tissue excised.

% of total breast volume excised	% patients in whom MCF would be left behind
10% (~lumpectomy)	60%
25% (~quadrantectomy)	50%
50%	23%

However, when only those breasts which actually harboured MCF were considered, then 95% of breasts (18/19) had MCF beyond 10%, 79% of breasts (15/19) had MCF beyond 25% (a quadrant), and 37% of breasts (8/19) had MCF beyond 50% of breast volume including the tumour. Of the 15 cases that had MCF beyond the index quadrant, 7 were infiltrating, (5 IDC + 2 ILC), 7 were in-situ (6 DCIS + 1 LCIS) and 1 was ADH. The discrepancy (14 vs. 15) between the results of analysis in 2- and 3-dimensions is related to the fact that in one case the MCF was within the anatomical quadrant as conventionally defined in two dimensions, but was beyond 25% breast volume which included the primary tumour.

We then calculated the distribution of the 54 MCF found in the study within increasing volumes of breast tissue around the tumour. Tables 5 and 6 show these distributions for primary IDC and primary ILC tumours, respectively. They show that the number of MCF contained within 10%, 11-25%, 26-50% and >50% of the breast volumes around the tumour were similar, indicating that MCF are scattered throughout the breast. The histological type of MCF (non-infiltrating or infiltrating) also had similar distributions within increasing volumes of breast tissue around the tumour. After exclusion of ADH and LCIS, these results remained unchanged. Atypical Lobular Hyperplasia (ALH) was not detected in any of the sections.

Table 5: Number of MCF contained within increasing volumes of breast tissue around the tumour, in 27 cases with primary IDC

% breast volume around the tumour	MCF contained within that breast volume				
	Total No.	Histological type of MCF			
		ADH	DCIS	IDC	ILC
≤10%	8	-	5	3	-
11-25%	10	-	4	5	1
26-50%	13	1	5	7	-
>50%	5	1	2	2	-

Table 6: Number of MCF contained within increasing volumes of breast tissue around the tumour, in 3 cases with primary ILC.

% breast volume around the tumour	MCF contained within that breast volume			
	Total No.	Histological type of MCF		
		ADH	LCIS	ILC
≤10%	6	-	5	1
11-25%	2	-	1	1
26-50%	6	1	5	-
>50%	4	1	-	3

ADH= Ductal Hyperplasia with Atypia, DCIS= Ductal carcinoma *in situ*, ILCS= Lobular carcinoma *in situ*, IDC= Infiltrating Duct Carcinoma, ILC= Infiltrating Lobular Carcinoma, MCF=Multicentric focus

In breast specimens that had IDC as primary tumour, presence of multicentricity was related to tumour size. Four out of 12 breast specimens with tumours < 3cm harboured MCF, while 12 out of 15 breast specimens with tumours \geq 3cm harboured MCF ($p=.02$). However, the actual number of MCF present in each breast or their distance from the edge of the primary tumour were not related to the tumour size. The volume of breast, expressed as percent of the total breast volume, which would be required to be excised to remove all MCF, also did not correlate with the size of primary tumour. MCF were present beyond 25% of breast volume including the tumour in 7/15 breasts with primary tumour <3cm and in 8/15 breasts with primary tumour \geq 3cm. There was no relationship between nodal status, age or menopausal status of the patient and MCF (their presence, actual number, distance from tumour edge, or, the percent volume of breast tissue that would be required to be excised to include it with the excision of primary).

Discussion

We found that 63% of our patients harboured multicentric foci in addition to the primary tumour. This incidence is

similar to that found by other workers using the Egan's technique (Lagios[Lagios, 1977], n=211: 56%, Egan[Egan, 1982], n=118: 69% and Holland[Holland et al., 1985], n=282: 63%). Although in our study, breast specimens with primary tumours ≥ 3 cm were more likely to harbour MCF than those with smaller tumours ($p=0.02$), there was no relationship between the tumour size and either the number of MCF or their distances from the tumour edge. When calculated according to breast volumes, there was no correlation between tumour size and the volume of breast tissue that would need to be surgically excised to include all MCF (expressed as % of total breast volume). There was no relationship between the histological type of MCF (whether infiltrating or in-situ) and the distance of MCF from the tumour edge or percent volume of breast tissue that would be required to be excised to include the MCF with the primary tumour (tables 5 and 6). Age or menopausal status of the patient were not related to the presence, number or distance of MCF from the tumour edge.

It is noteworthy that although radiography detected 33% of the MCF, they were missed in 52% of cases. Our findings regarding the distribution of MCF around the primary tumour, expressed as distances from the tumour edge, are

similar to that of Holland et al, [Holland et al., 1985](Table 2). We found that 53% of patients had MCF within 2cm, 80% of within 4cm and 90% within 5cm of the tumour edge. The difference between our study and that of Holland et al (1985), however, lies in the fact that the latter group did not take the size of the breast into account, and expressed the distribution of MCF in only one dimension. Expressed in this way, in one dimension, an impression is created that MCF are mostly present around the primary tumour. Our approach to the analysis in 2- and 3- dimensions makes the following novel observations. 1) The relative distribution of primary tumour and MCF in the 4 breast quadrants was significantly different ($p=0.034$). We found that the primary tumour was more common in the upper outer quadrant while MCF were widely distributed in all 4 quadrants, suggesting that MCF are widely scattered throughout the breast. 2) When the 19 breasts that actually harboured MCF were considered, in as many as 79% (15/19) MCF were present beyond 25% of breast volume including the tumour (index quadrant). When all patients were considered, half (15/30) harboured MCF beyond the index quadrant. Thus, even if a quadrant were excised, 50% of patients would still have MCF left behind.

The above findings are at variance with the suggestion made by Holland et al that MCF are present in the index quadrant in close proximity of the primary tumour in 90% of cases and therefore could be responsible for local recurrence. Is our sample size of too small and our findings a result of play of chance? Let the hypothesis be, as has been suggested by Holland et al (1985) that in 90% of cases MCF are contained within the index quadrant. If this hypothesis were true, then 25% of breast volume including the tumour would contain all MCF in 90% of breast specimens. Thus, we should have found all MCF within 25% of breast volume in 27 of the 30 (90%) breast specimens. In actual fact, we found that all MCF were contained in the index quadrant in only 15 of 30 (50%) breast specimens. The probability of our finding being due to play of chance is 1 in 1500 (27:3 vs. 15:15, chi sq. =11.4, p=0.0007).

Our finding that MCF lie beyond the index quadrant in 50% of breast specimens may have implications for breast conservation therapy (BCT). In large series of breast conservation studies, it has been seen that >90% of early breast recurrences occur in the quadrant that harboured the primary tumour ([Harris et al., 1981], [Clark et al., 1982], [Schnitt et al., 1984], [Clarke et al., 1985], [Kurtz

et al., 1989b], [Boyages et al., 1990], [Fowble et al., 1990], [Fisher et al., 1992], [Clark et al., 1992], [Veronesi et al., 1993]). This is true whether or not radiotherapy is given ([Clark et al., 1992]). If recurrences were to arise from MCF, then we would expect 50% of recurrences to occur in other quadrants. Since this is not the case, we conclude that early recurrences do not arise from MCF. Therefore, MCF in the index breast should behave in a fashion similar to putative MCF present in the opposite breast. This is borne out by the fact that recurrence rate in the remaining quadrants of the index breast is identical to that in the opposite breast (1% per year in both cases,[Kurtz et al., 1989a]). We believe that recurrences in the index quadrant arise from a) the original primary tumour cells left behind, b) a new disease arising as a result of chromosomal instability, or c) from circulating metastatic cancer cells lodging in the highly vascular bed of the excised tumour. The latter is supported by the fact that patients who have local relapse in the breast after BCT have a relatively poor prognosis ([Fisher et al., 1991b], [van Dongen et al., 1992]).

In any case, if multicentric foci (MCF) do not give rise to breast recurrence then why should we treat them with

either mastectomy or whole breast radiotherapy? It is as necessary or as unnecessary as treating the contralateral breast! It appears that local treatment of breast cancer could probably suffice to be truly local- at and around the site of the primary tumour!

Summary

We studied the spatial relationship within the breast between multicentric foci (MCF) and the primary tumour in 30 modified radical mastectomy specimens using Egan's correlated pathological-radiological method using 5mm slices of the whole breast. The relative positions within the breast of the primary tumour and MCF were used to calculate the relative distribution of primary tumour and MCF in the 4 quadrants of the breast and the percent breast volume that would be required to be excised to include all MCF. Nineteen (63%) breasts harboured MCF. The relative distribution of primary tumour and MCF in the 4 breast quadrants was significantly different ($p=0.034$). MCF were present beyond the index quadrant (25% of breast volume including the tumour) in as many as 79% (15/19) of breasts that harboured MCF; and, in half the cases (15/30) when all breasts were considered. This is in variance with the suggestion put forward previously that MCF are contained within the index quadrant in 90% of cases. Although the number of patients in the present series is small, the probability of our finding being due to play of chance is 1 in 1500. In large series of breast conservation

studies >90% of early breast recurrences have been found to occur in the index quadrant. Our finding, that in half the patients (15/30) MCF are present in quadrants other than the index quadrant, suggests that MCF do not give rise to early breast recurrence.

CHAPTER 3

Can magnetic-resonance imaging detect the clinically relevant multicentric foci?

Introduction

We have shown that when mastectomy specimens are examined by detailed radiological-histological correlational methods, small additional invasive or in-situ cancer foci are found in over 60% of patients; 80% of these lie remote from the index quadrant[Vaidya et al., 1996]. Since 90% of local recurrences occur in the index quadrant, we have questioned the clinical relevance of these small cancer foci that remain dormant for a very long time.[Baum et al., 1997]. Since most of these small cancers may not cause clinical cancers and endanger the patient's life we wished to investigate whether there is any non-invasive and pre-operative test that might reveal which of these dormant cancers are clinically relevant.

Angiogenesis is a prerequisite for tumour growth beyond 1–2 mm in diameter and is directly correlated with poor prognosis. [Weidner et al., 1991]. Unlike radiography that relies on tissue density for detecting cancers, magnetic resonance imaging (MRI) relies on tumour vascularity and vascular permeability[Buadu et al., 1996], as demonstrated

by contrast enhancement. MRI is highly sensitive for breast cancer detection but its specificity is relatively low[Heywang-Kobrunner et al., 1997]. We hypothesised that if any of these occult tumours were detectable by MRI, then these would be the ones that were potentially more dangerous. In that case, we would be able to geographically map these “more dangerous” tiny tumours and tailor treatment accordingly. We therefore tested how many of the occult tumours that are detected by the detailed radiological-histological method were detected by MRI.

Method

We evaluated prospectively whether small enhancing foci, seen separately from the main tumour on contrast-enhanced MRI, were indeed cancer foci and whether MRI could detect all cancer foci identified by radiological-histological correlation. We studied ten patients. All patients underwent preoperative contrast-enhanced breast MRI. High resolution transverse T1-weighted 3D FLASH images (TR=18 ms, TE=7 ms, FA=40°, TA=4 m 56 s, FOV=410 mm) before and after an intravenous bolus hand injection of dimeglumine gadopentetate (Magnevist, 0.2 mL/kg)

were acquired at 1.0 T (Siemens Magnetom Scanner 42 SP with dedicated breast coil). The 3D volume was 64 mm thick with 32 partitions giving an effective slice thickness of 2 mm and this was sufficient to cover the entire breast in all cases. All patients underwent surgery for the breast cancer. Modified radical mastectomy was performed in four patients and wide local excision in six patients.



The surgical specimens were fixed and sliced at 5 mm intervals in the same plane as the MRI. An experienced breast pathologist performed routine histopathological examination and the remaining material was radiographed. Two observers (Jayant Vaidya and Michael Douek) identified radiological abnormalities (calcifications, densities, or spiculations) and all lesions that were deemed suspicious by either observer were mapped on to the specimen, sampled and examined histologically. A specialist radiologist

(Margaret Hall-Craags) reviewed MRI images independently and findings were compared with histopathology results.

Results

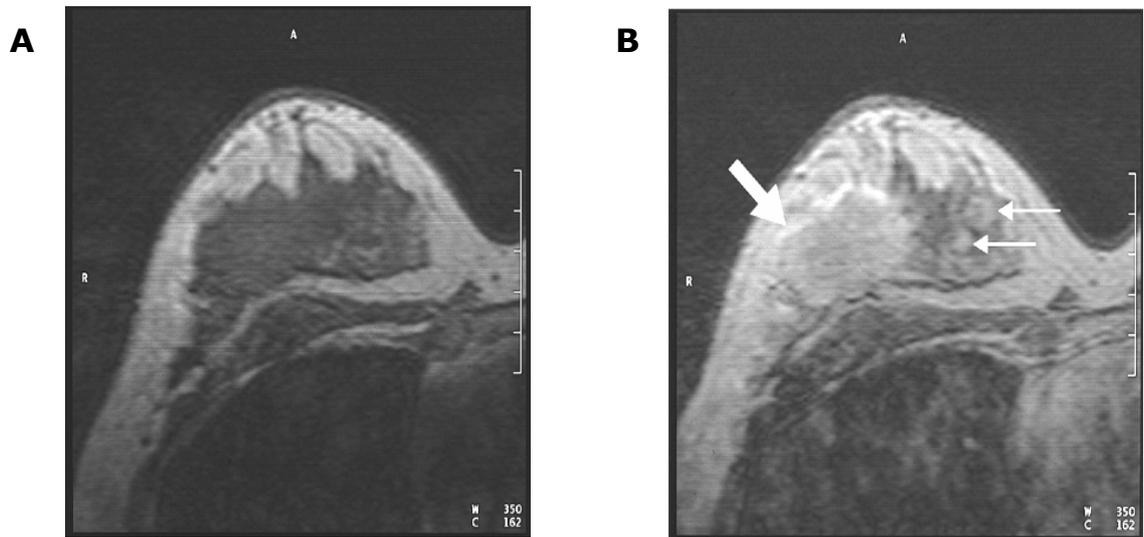
On MRI, 19 enhancing foci separate from the main tumour were identified in seven out of ten patients (figure). On radiography of specimen slices, 71 suspicious areas were sampled and histological examination revealed 15 areas of 'occult' cancers in five patients. Of these 9 were in-situ and 6 were invasive cancers. All five patients with cancer foci on histopathology were amongst the seven patients who had enhancing foci on MRI. In two of these five patients, the tumour was surrounded by widespread enhancement on MRI and all 11 (four+seven) areas sampled showed cancer foci. In all wide local excision specimens, the enhancing foci on MRI were within 11 mm of the tumour edge and therefore within the resected specimen.

MRI		Number of patients	Number of foci
Separate MRI foci absent (3)	No enhancement	3	0
Separate MRI foci present (7)	Focal enhancement	5	8
	Multiple enhancing foci	2	11*
Total		10	19*

*In the 2 patients with multiple enhancing foci, all 11 histological samples were found to harbour invasive or in-situ cancer and a count of 11 was awarded to MRI for comparison with histology.

Histology		Number of patients	Number of foci
Separate histological foci absent (5)		5	0
Separate histological foci present (5)	DCIS only	2	5
	IDC only	1	1
	IDC + DCIS	2	5 IDC + 4 DCIS
Total		10	15

N.B. Thus 5 specimens showed separate foci on histology- all these were had shown enhancement on MRI.



T1-weighted breast MRI before (A) and after (B) contrast-enhanced MRI
-Two separate enhancing foci (small arrows) are visible away from the primary tumour (large arrow) after contrast enhancement.

Discussion

Our data suggest that enhancing foci on MRI represent cancer foci and that MRI detected 14 out of 15 cancer foci (sensitivity 93%). Of course, this is based on the assumption that the radiological-histological correlational method is indeed the gold standard. If that is so, the specificity of MRI for tumour detection would be 79% (15/19). However, bearing in mind that the spatial resolution of MRI is of the order of 1–2 mm, it may yet transpire that MRI could have even greater sensitivity and

specificity that may become apparent with an even more obsessive sampling of the specimen.

Our findings provide strong circumstantial evidence that small enhancing foci on MRI represent cancer foci and that MRI is highly sensitive for the detection of invasive or in-situ cancer foci.

This was contrary to our hypothesis that MRI might detect only a subset of the occult cancers in the breast- mainly those that might have stimulated local angiogenesis and are therefore more vascular. We thus realised that MRI might not be able to identify a subset of occult tumours that are clinically relevant allowing us to selectively treat patients. We found that MRI on the other hand is highly sensitive in detecting multicentric foci. Finding these enhancing foci on pre-operative MRI may prompt many a surgeons to advise their patients to undergo a mastectomy. The number of MRI machines is increasing worldwide and the additional cost of a breast coil is insignificant compared to the cost of the MRI. So we fear that when MRI is used for pre-operative evaluation in breast cancer, many unsuspecting women will be found to have these 'enhancing foci' in their breasts. The surgeon will be in a dilemma and

to be on the safe side might advise a mastectomy to a woman who might otherwise safely have had a breast conserving therapy, reversing the trend of the last 30 years.

On the other hand, the high sensitivity of MRI could be used more constructively. Our results suggest that MRI could be used to investigate prospectively the clinical significance of unresected cancer foci in order to convincingly determine their natural history in the context of breast conserving surgery. A study in which women found to have enhancing foci on MRI but have no other evidence of multicentric tumours on clinical or radiological grounds are prospectively followed up, would be deemed ethical because breast MRI is still considered experimental for preoperative planning of surgery. In a few years we might be able to ascertain whether any of these latent occult tumours progress to an actively progressive phenotype.

CHAPTER 4

The novel technique of intra-operative radiotherapy

Introduction

We have used a novel technology to deliver therapeutic radiation. The technique employs a miniature electron-



beam driven x-ray source (the Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA) that delivers low energy (50Kv) x-ray radiation directly to the tumour site/ tumour bed from the tip of a 10cm long, 3.2mm diameter, tube. Being soft x-rays, there is quick attenuation of the radiation within tissues so that the dose is

inversely proportional to the 3rd power of the distance. Such quick attenuation reduces the damage to surrounding normal tissues and minimises the need for radiation protection to the operating personnel. The x-ray production itself is controlled very precisely and monitored in three ways – one within the X-ray source, one kept on the operating theatre table and third using thermo-luminescent detectors (TLDs). The portability of the device enables radiation treatments to be delivered precisely and directly to the inside of tumours, or the tumour bed, while at the

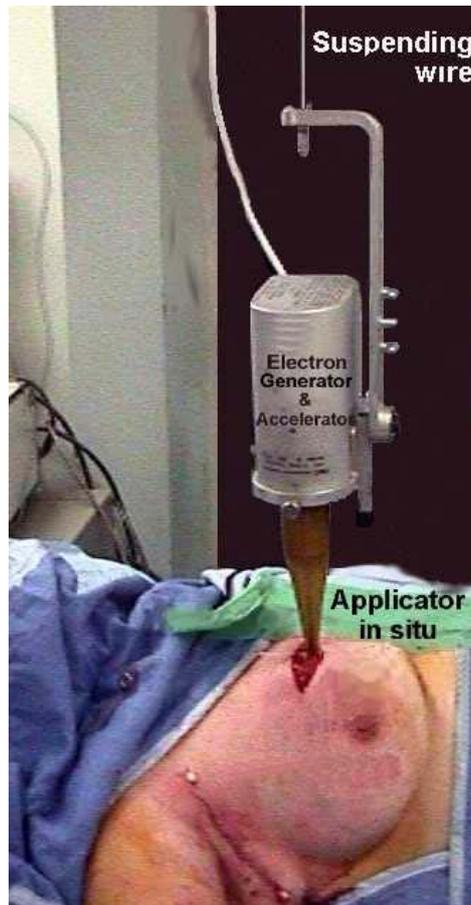
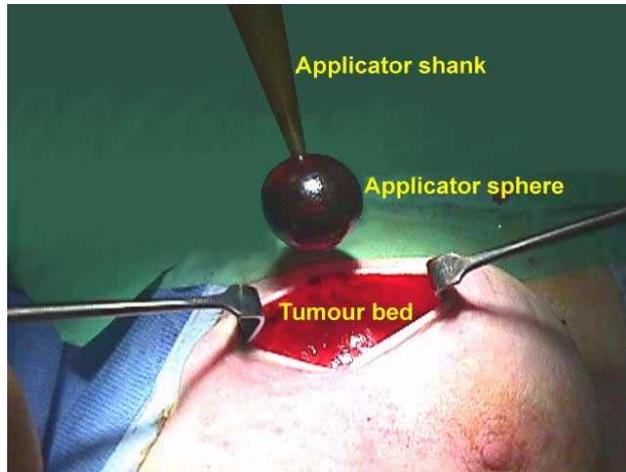
same time, minimising unwanted irradiation of surrounding tissue.

Since the radiation consists of soft X-rays, the beam is rapidly attenuated to reduce the dose to more distant tissue. Full measurements and calibration are carried out in a water phantom and in materials that simulate the radiation absorption properties of the breast. Depending upon the size of the surgical cavity, various sizes of applicator spheres 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 depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimise the radiation treatment. For example, a dose of about 5 Gy can be delivered in about 20 minutes at 1cm 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 x 11 x 14 cm; applicator: 16 cm long conical applicator sheath with a 2 to 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, which 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 simple, effective technique avoids the unnecessarily complex and sophisticated techniques of using interstitial implantation of radioactive wires to provide high dose radiotherapy to the tumour bed or the even more complex techniques necessary for conformal radiotherapy by external beams with multi-leaf collimators from a linear accelerator. The quick attenuation of the radiation dose allows the treatment to be carried out in unmodified operating theatres. The walls usually incorporate shielding for microwave radiation from electronic equipment such as mobile phones and such walls provide enough protection to the staff. Furthermore, the biologically effective dose (BED) attenuates rapidly so that the highest radiation dose is received by tissue nearest the primary tumour and a much lower dose at the skin. Thus in theory, the biological effect and cosmetic outcome could be improved.

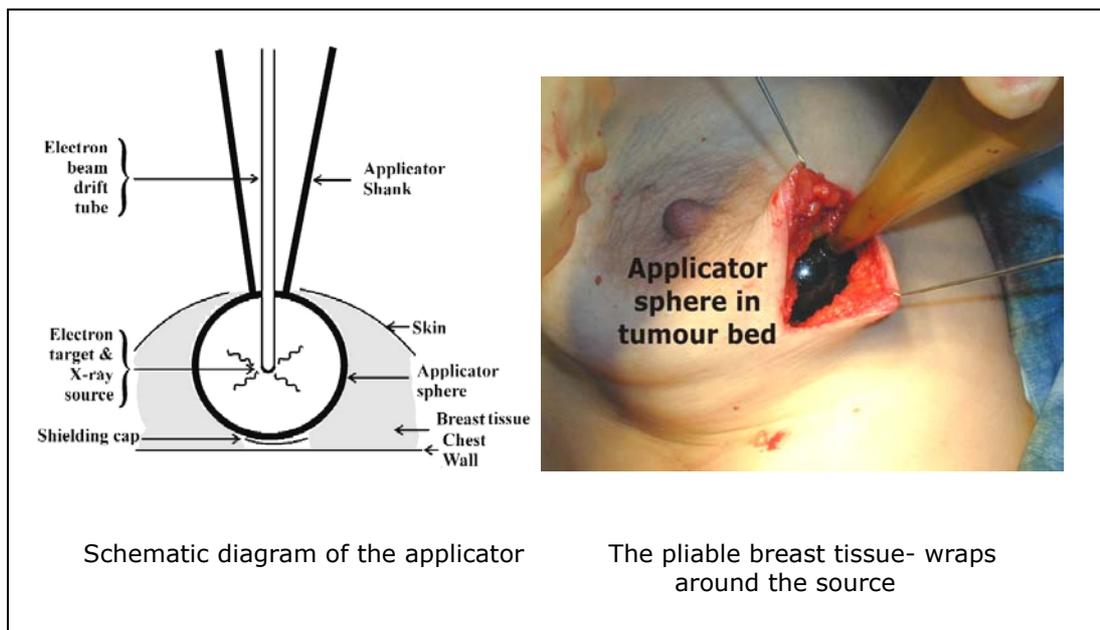
These are the photographs of the first case on 2 July 1998



The Physics and Radiobiology

The miniature x-ray source (XRS) developed for the Photon Radiosurgery System contains a proprietary miniature x-ray tube, a high voltage power supply, and the associated electronic circuitry required to control and monitor the operation of the x-ray tube.

The distal end of the x-ray tube is a thin probe extending



outside the XRS enclosure. X-rays are emitted from the tip of the probe, which is inserted into the site to be irradiated. Within the XRS, an electron gun accelerates electrons towards a gold target at the tip of the probe.

The last 2cm of the probe are made of beryllium, an x-ray transparent material. When the electrons strike the target,

x-rays are generated in a nearly spherical distribution centred at the tip of the probe. The x-ray tube (XRT) is a miniature electron gun and electron accelerator. Electrons are generated and accelerated towards a gold target at the end of a long, thin drift tube or probe. The operation of the x-ray tube requires that the filament be heated which, in turn, heats the cathode and an excess of electrons is generated by thermionic emission. Electrons produced by the gun are accelerated to the desired energy, and with the help of steering coils, directed down an evacuated field-free tube towards a thin, gold target. Anodes located in the electron gun assembly provide the accelerating potential of the electron beam. The vacuum envelope of the system is composed of a brazed metal/ceramic structure for good thermal and mechanical shock tolerance. The electron optics of the device are designed to provide a highly focused, stable spot of electrons at target. Following acceleration, the electrons enter a 10cm long, 3mm diameter "needle" type, evacuated drift tube. The drift tube or probe passes through the deflection coils and is terminated with a beryllium (Be) window that is transparent to x-rays. The electron beam is directed to a point on the target. When fast electrons interact with matter, part of

their energy is converted into electromagnetic radiation in the form of characteristic and bremsstrahlung radiation. The fraction of the electron energy converted into bremsstrahlung increases with increasing electron energy, and is largest for absorbing materials of high atomic number (the atomic number for gold is 79). This is the same process that results in the production of x-rays within conventional x-ray tubes. The result of this is the production of a symmetric distribution of radiation around the tip of the probe.

The physics, dosimetry of this soft x-ray device have been well studied and the probe has already been tested in pre-clinical studies.

Radiobiological experiments [Astor et al., 2000] using cell cultures have suggested that the radiobiological effectiveness (RBE) of the PRS system is between 1.2 and 2.5. This was in agreement with microdosimetric analysis and modelling [Brenner et al., 1999]. The PRS radiation is found to induce both necrotic and apoptotic cell death in addition to rapid cell death through non-apoptotic pathway.[Kurita et al., 2000]. Animal experiments have demonstrated that PRS can induce well demarcated ablation in canine liver and kidney[Koniaris et al., 2000;Solomon et al., 2001].

Thus, the characteristics of this radiation are:

- **Low energy x-rays** (50keV maximum) used to ensure minimal radiation dose to adjacent normal tissues and critical structures.
- **Low voltage supply**, approximately 12V, ensures no electrical hazard to the operator.
- The XRS is **lightweight and portable**, which makes it easily adaptable to any clinical application.
- The low energy x-rays produced by the XRS are easily shielded, and there are **minimal radiation protection requirements** in the operating room.
- The PRS has been cleared by the FDA after the report of this project, to be marketed for radiotherapy anywhere in the body and also carries a CE Mark allowing it to be marketed in the European Community for radiotherapy applications.
- We have developed a range of applicators from 2.5cm to 5cm for use in the breast, as detailed in the next section.
- A range of special Quality Assurance



tools is supplied with every system to ensure maximum safety and ease-of-use. These are necessary as a result of the x-ray source's unique treatment geometry.

The radiation dose at various distances from the cavity margin varies as shown in the table, for the simulated assembly.

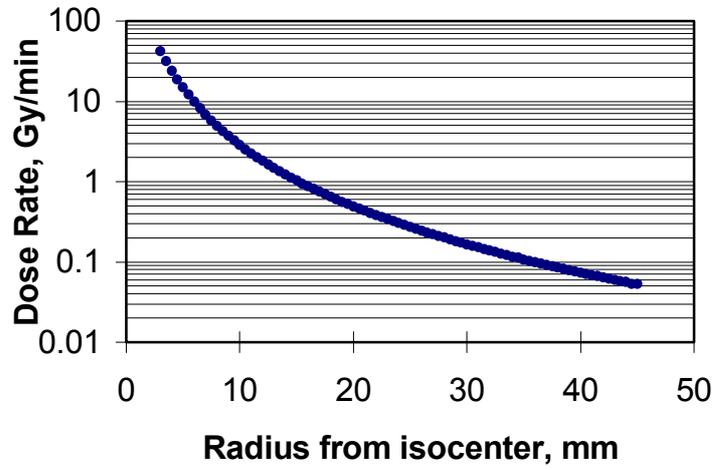
Standard dosimetry table: Calculations for a 3.5 cm diameter spherical applicator and a period of irradiation of 21 min as measured from the periphery of the sphere in a breast phantom. (PRS operating parameters:50Kv)

Distance from the surface of the applicator	PE probe (Gy)		External beam radiotherapy (Gy)		Whole breast radiotherapy (Gy)	
	PD	BED	PD	BED	PD	BED
0.1 cm	15	165	10	12	50	60
0.2 cm	12.5	121	10	12	50	60
0.5 cm	8.75	59	10	12	50	60
1 cm	5	21.7	10	12	50	60

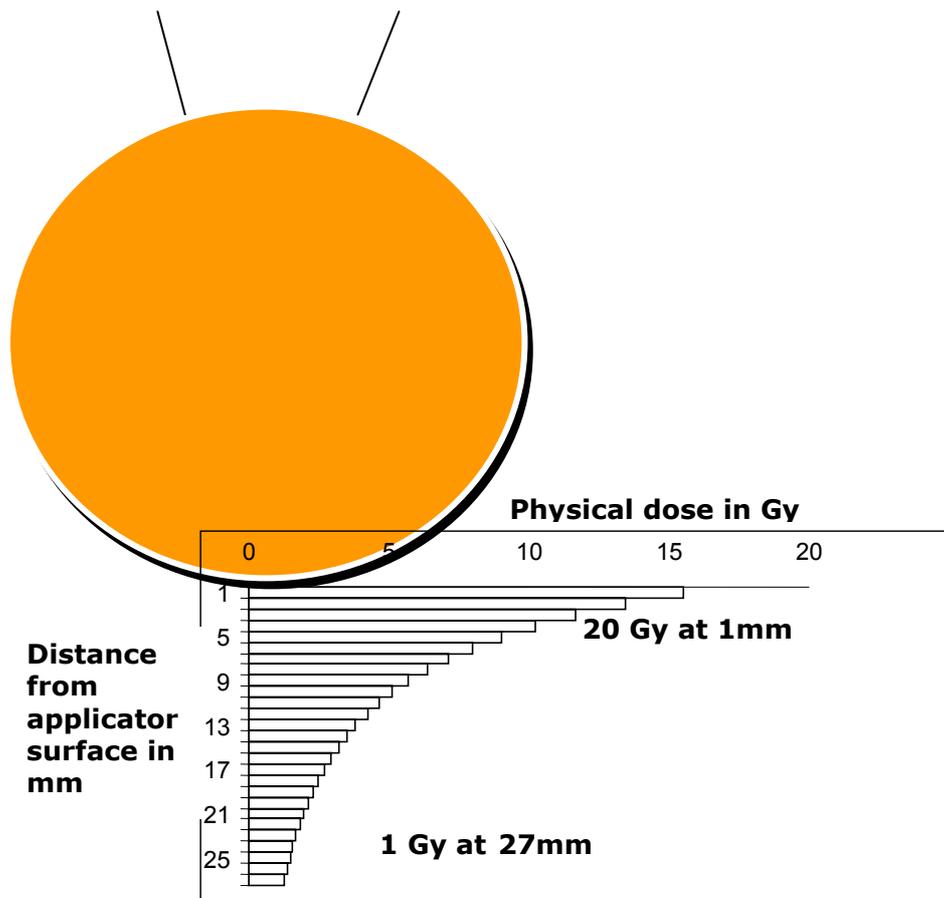
PD= Physical x-ray dose, BED= Biologically effective dose, .

The biologically effective dose (BED) is given by the equation (Dale 1985), $BED= D \times (1 + (d/(\alpha/\beta)))$, where D is the total physical dose, d is the physical dose per fraction and α/β is the biological coefficient which is 10 for early and tumour effects when radiotherapy is delivered in fractions of about 2Gy. For a single dose, we have assumed the value of α/β to be equal to 1.5. It could actually range from 1.5 to 4.

Dosimetry around the bare probe in water (in terms of dose rate)



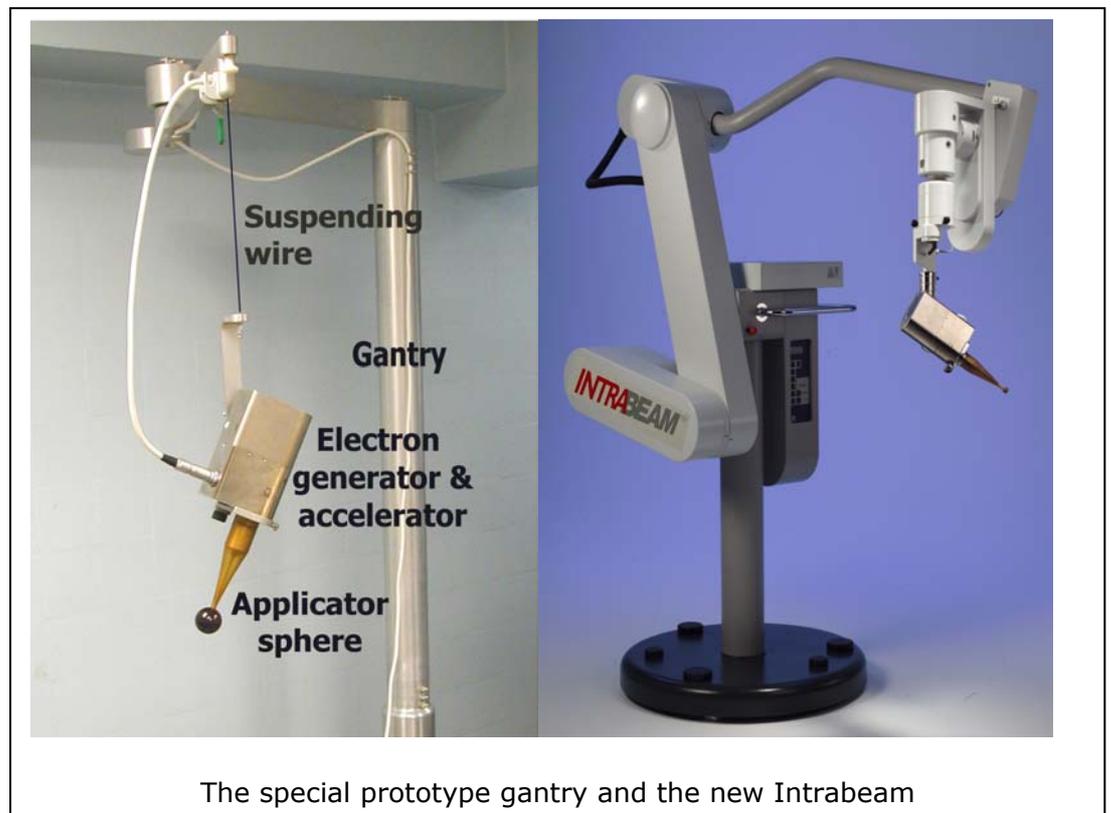
Dosimetry around the applicator (in terms of physical dose with a prescription of 5Gy at 1cm)



Positioning the X-ray source

It is important that the x-ray source (XRS) is very stable and does not move at all during the treatment. It was thought that the movement of the chest wall during respiration would cause enough displacement of the x-ray source and the applicator within the tumour cavity to jeopardise the correct dosimetry. Hence a special suspending gantry was designed.

This is a large gantry that suspends the XRS with the help



of a hydraulic counter-balance system such that it remains stable in any position that it is placed. While doing treatments, it was noticed that in actual fact, there is hardly any movement of the XRS during normal respiration and therefore there is no need for the large, heavy and awkward gantry. A simple arm to fix the XRS to the operating table would be adequate. Subsequently, the PeC Company established a strategic alliance with Carl-Zeiss and the commercial device uses a multi-armed device to hold the XRS in position the system being called INTRABEAM.

Development of the machine for Brain tumours

The machine was originally developed for the treatment of brain tumours using stereotactic frames. This development started in 1992 and the machine was used for treatment of brain tumours since 1994. [Butler et al., 1998;Cosgrove et al., 1997;McDermott et al., 1996;Douglas et al., 1996] [Cosgrove et al., 1997;Cosgrove et al., 1999]

Conceptualisation and adaptation for the breast: use of special applicators

In the spring of 1996, we began a dialogue with the company to adapt the machine for use in the breast. This

would need to adapt the technique for use in a very different part of body. As opposed to the brain, where there are bony landmarks whose relationship to neural structures is relatively fixed, breast is a very mobile organ. There are no structures - reference points - that have a constant relationship to a tumour bed. We felt that movement of the chest wall during respiration would also change the configuration the chest wall enough to make a significant difference. So we had to apply a different strategy. Firstly we assessed the shape of the cavity.

Shape of the cavity after wide local excision

We assessed the shape of the cavity after wide local excision using a fast setting wound dressing material (Cavicare®). Within 15-20 seconds of mixing the two components the foam that is placed into the cavity starts setting and within 1-2 minutes, the cast of the cavity can be removed to be studied. We found the shape of the cavity to be rather irregular; nevertheless the shape was that of a multisided pyramid with the base resting on the posterior/deep wall. We also realised that this cavity could easily be made spherical if the pliable breast tissue were wrapped around a rigid applicator so that the tissue

immediately beyond the surgical excision would be closely applied to the surface of the applicator and thus get the highest dose of radiation.

The technique of giving intra-operative radiotherapy

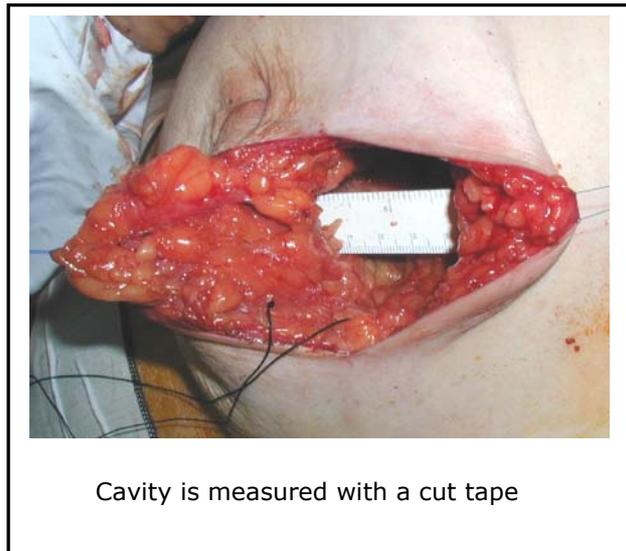
Sterilisation issues

In the first few cases using the Photoelectron's Photon Radio Surgery (PRS) X-Ray Source (XRS), we sterilised the whole X-ray source. This was done using Plasma sterilisation. Sterilising the XRS meant that it had to be delivered to the Central Sterilisation Department at least 24 hours in advance and, when it was returned, it needed to be re-calibrated in the sterile atmosphere of the operation theatre by the medical physicists team dressed in sterile gowns and gloves. This took about 1 hour of additional time of the physicists on the day of the surgery. After the first few cases, we also found that the tip of XRS accumulated an oxidative product of Molybdenum viz., Molybdenum trioxide. Molybdenum trioxide is potentially toxic - irritant to eyes and upper aero-digestive system and there is some evidence of its carcinogenicity in mice and male rats. A solution to these problems was to enclose the XRS in a

large sterile plastic bag. We used a large transparent plastic bag (38.1cm x63.5cm x99cm or 15x25x39 inches, 40 μ thick) with a pleat on either side- that is ubiquitous in our operation theatres, easy to sterilise and costing almost nothing. The XRS was calibrated on the previous day at the convenience of the medical physicists and kept unsterilised. The applicators were sterilised, each in separate covers. During surgery, the sterile plastic bag was modified- a hole was cut at its bottom - to accommodate the applicator sphere. Then, the applicator was inserted in plastic bag such that the sphere protruded out of it and the conical sheath remained inside the bag. The edges of the newly created hole were now sealed with sterile tape to the junction of the applicator globe and shaft. The bag was then inverted inside out. The XRS was now lowered into the applicator and locked in and the power supply cord attached. The bag was now lifted over the XRS so that it covered the XRS. The bag was kept in place with sterile plastic tapes. This procedure of covering the XRS was inspected and approved by the Consultant Microbiologist. This adaptation considerably reduced the time the physicists needed to spend in the operating theatre.

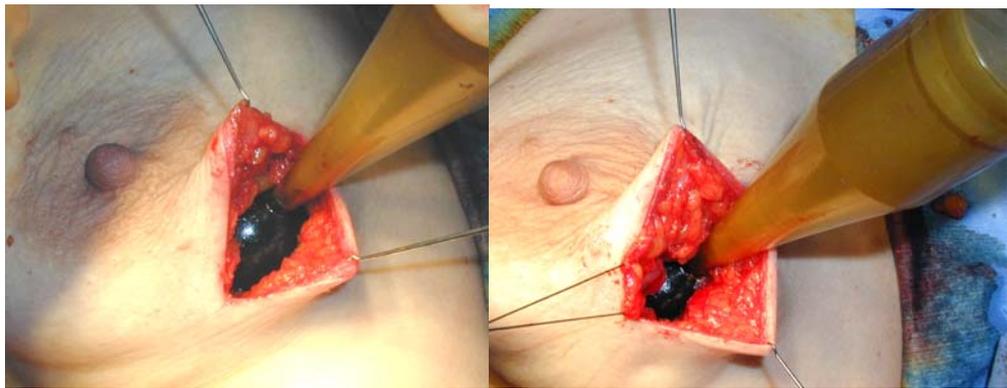
Operative technique

A single prophylactic dose of intravenous antibiotic (Cefuroxime 1.5gm) is given at induction of anaesthetic.



The wide local excision (WLE) is carried out the usual way and immaculate haemostasis achieved. The depth of excision always includes the pectoralis fascia so that there is no breast tissue beyond the deep margin. This is especially important on the left side. One or two gauze pieces are left in the breast wound and axillary surgery is performed. This consists of either the usual axillary dissection or sentinel node biopsy, alone or in combination with axillary dissection as part of another ongoing clinical trial.

Haemostasis of the breast wound is now rechecked. This is very important since, even tiny ooze from capillaries can collect significant amount of blood over the duration of radiotherapy and this could potentially cause a distortion of

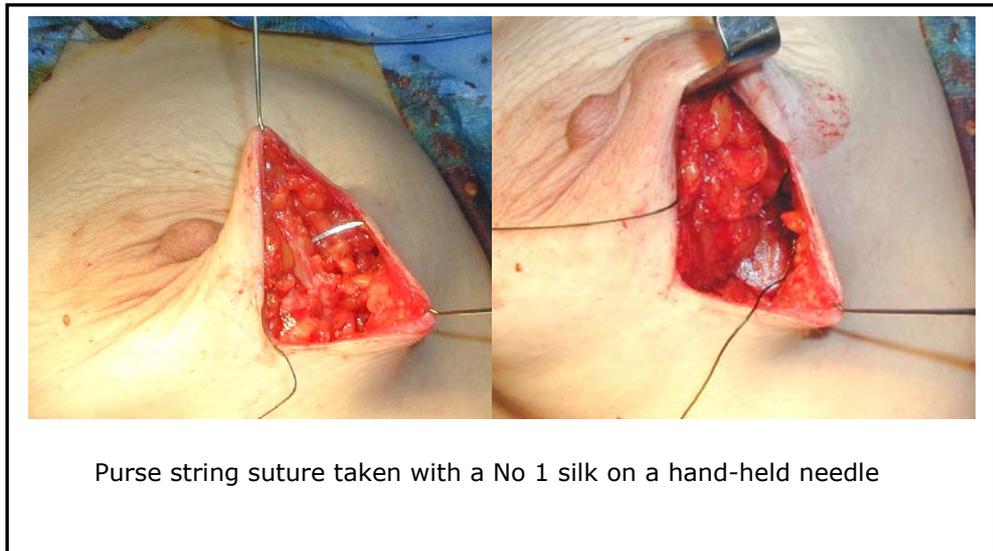


The applicator is inserted in the cavity to assess the closeness of fit

the cavity around the applicator. Distortion of the cavity can change the dose that the target tissues receive. In addition we have found that the temperature of the cavity rises by 2°C from an average of 32°C that is present in the operative cavity in the operating theatre. This increase in temperature could dilate the blood vessels and cause an ooze. The diameter of the cavity is now measured with a disposable tape measure cut to 4cm or 5cm. This and the judgement of how well the breast wraps around the applicator – actually inserting the applicators in the wound

and visualising the apposition is very useful – will determine the size of the applicator. The usual size of the applicator is either 3.5, 4 or 4.5 cm. We have used the 3 or 5cm applicators only a few times.

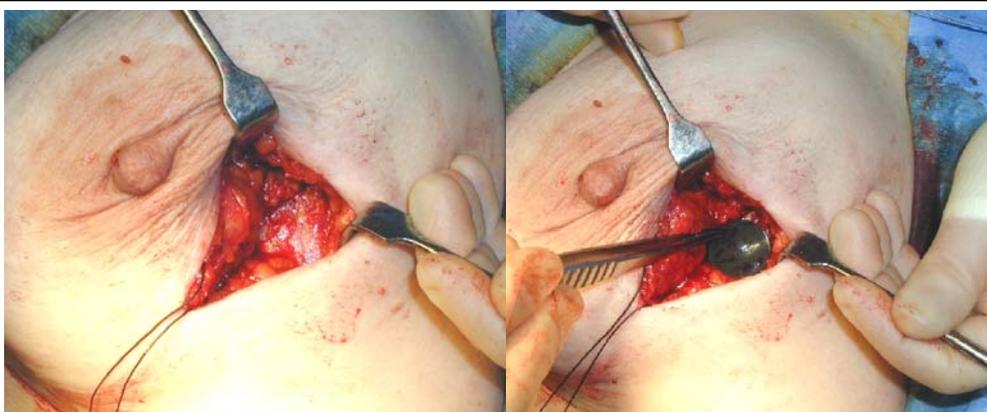
A purse-string suture is now taken with a No 1 silk mounted



on a hand-held needle. This step is very important and needs to be taken very carefully because the dose to the target tissues depends on how well it is taken. This stitch should be taken deep to the whole cavity edges, through the breast tissue and not in the subcutaneous tissues, such that on tightening the purse string, the skin should not get pulled too close (<1cm) to the applicator; at the same time, on pulling the purse-string, the breast tissue should appose to the surface of the applicator and wrap around it. It is important to visualise and ascertain during this phase,

how well the target breast tissues appose to the applicator surface. It adheres naturally.

If the tumour is on the left side, a tungsten-impregnated rubber shield is used to cap the applicator, to protect the heart and coronary vessels. The applicator cap needs to be positioned such that it apposes the bare muscle on the



Tumour cavity in a left breast – and the shield being placed on chest wall

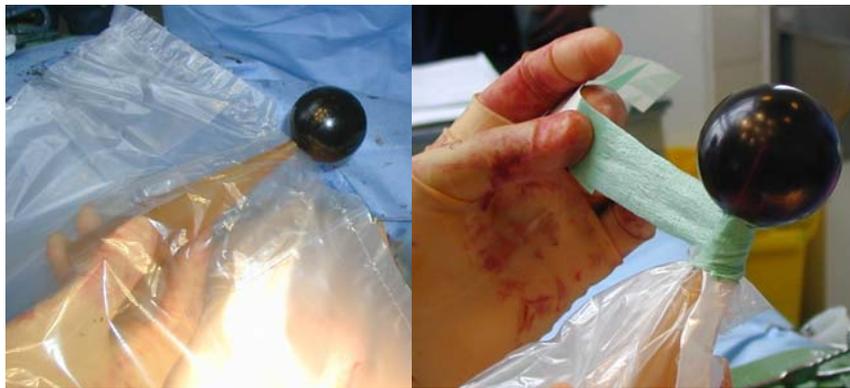


Distance from applicator to skin

chest wall.

Since the Intrabeam device is not sterile, it is wrapped in a sterile polyethylene bag. At first, a hole is cut at the closed end of the bag for the applicator sphere to come out which is taped at its neck.

The bag is now turned inside out. Once the purse string and position of the gantry is ready, Intrabeam is attached to the

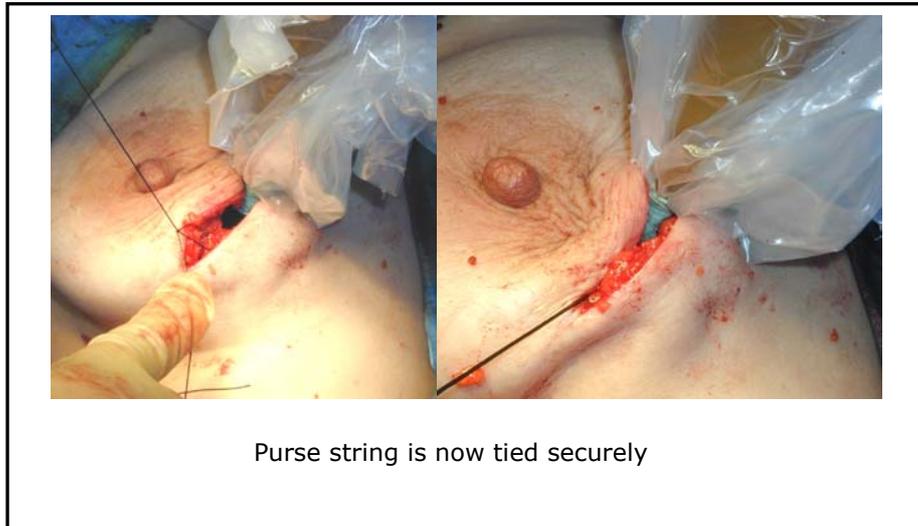


Applicator is wrapped in sterile polyethylene bag and taped



The X-ray source is being inserted into the applicator

applicator and the bag reversed over the Intrabeam to cover it- and taped in place. In the commercial device- modelled over this prototype is now available with pre-designed holes and tapes to cover the Intrabeam device. Once the applicator is in place, the position of the chest wall shield is ascertained, the purse string is tightened carefully. Care is taken to ensure that all breast tissue in the cavity apposes applicator and no part of skin is less than 1cm from the applicator.





The whole assembly



Frequently the skin edge flips over the applicator. In order to avoid this getting excessive radiation dose, a 3-0 Prolene stitch is now taken in the dermis of the skin edge in order to pull it away from the shaft of the applicator so that it

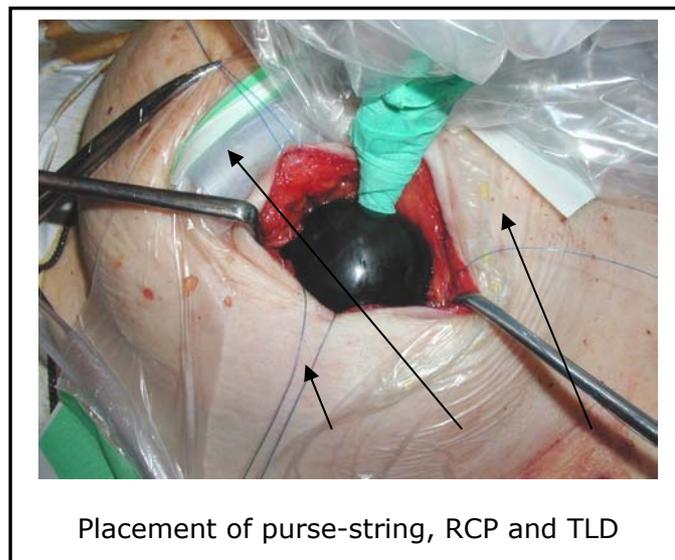


does not come in direct contact with the applicator or in direct line of the applicator with only an air gap in between. The minimum distance between skin at the site of TLD/RCP and the applicator is measured. All care is taken that this is not less than 1cm. If the cavity is such that the best positioned purse string still draws one part of the skin too close to the applicator then a small piece of gauze soaked in saline, and 0.5cm to 1cm thick is inserted between the skin and applicator such that the gap between the applicator surface and the skin is at least 1cm. If the tumour is very superficial we have preferred to take a small

ellipse of skin that might be involved - as would be the normal oncological practice.

Three Thermo-Luminescent Detectors (TLD) and a sheet of Radio-chromatic paper (RCP) is placed adjacent to the skin edges and kept in place with transparent tapes.

When the XRS is lowered into the breast wound we have found that lowering the operation table to the lowest level, helps in balancing the XRS in the most stable position. The



position of the XRS should be usually vertical and stay in its position once it is left free to hang. Once the XRS and the applicator is inserted and well balanced, a Tungsten impregnated sheet covers the wound around the applicator. This blocks 95% of radiation and reduces the amount of radiation in the operating theatre to very low levels and that in the corridor to near zero levels.

The anaesthetist wearing a lead gown sits behind a portable lead shield and the physicists are located just outside the operation theatre, along with the portable computer and monitoring equipment. The surgeons and nurses un-scrub



and go out of the theatre.

Once the radiotherapy is completed, the shield is removed, the purse-string cut and the XRS delivered to the Physics team. The TLDs and Radiochromatic paper is handed over carefully mapping the position of each of the TLD.

Haemostasis is confirmed and wound closed. We used a 2-0 prolene subcuticular stitch in early cases, leaving it for 14 days before removal. Since the last year we have used 3-0 monocryl absorbable monofilament suture which is

absorbable and does not need to be removed, but the steristrips are left in place for 14 days, unless there is need to remove them earlier.

The axillary wound is always drained with a Redivac drain and the breast wound sometimes drained, the choice based on individual patient. The breast drain is removed within 24 hours to reduce the chance of causing a puckered wound.

Giving IORT increases the operating time by 45 minutes on average (range 34 to 60 minutes).

The prescribed dose is 5Gy at 1cm. This delivers a physical dose of about 20Gy at the surface of the applicator. The time to deliver this dose depends upon the size of the applicator- generally larger the applicator, longer the duration. For a 3.5cm applicator, the time is usually 24-25 minutes and for a 5cm applicator is it is usually around 38 minutes. The radiation from the probe varies by a small fraction at every session and is calculated on site – hence the small range of durations even for the same size of the applicator.

Summary

- Assess the size
- Achieve meticulous haemostasis
- Prepare the applicator in the plastic bag
- Position the shielding cap if tumour on Left side
- Prolene stitches for reflecting skin edges if required
- Purse string in breast tissues
- Attach the applicator (already in plastic bag) to the XRS
- Lower the applicator in the wound – and pulling the purse string
- Adjust and ascertain close fit of breast-wrap-around the applicator
- Tie the purse string
- Reassess the closeness to skin etc
- Place the TLDs
- Place the shields over the wound
- After radiotherapy- reconfirm haemostasis and close the wound with subcuticular monocryl sutures.

Postoperative care

The postoperative care is not different from the usual. If there was a breast drain, it is removed at 24 hours and the patient is usually home after removal of drain within 3-6 days.

Radiation safety

The operation and radiotherapy are carried out in the usual operating theatres with no special shielding apart from the portable lead shield and lead aprons. The measurement of radiation dose on the anaesthetist's body is nearly undetectable.

CHAPTER 5

The pilot study of intra-operative boost radiotherapy

Time course : events leading up to the setting up of the pilot study

After completion of the study of whole organ analysis of mastectomy specimens (Chapter 2) the paper was presented at the Hong Kong International Cancer Congress in November 1995. This was the time when I proposed that radiotherapy to the index quadrant alone is probably sufficient for early breast cancer.

The paper was submitted to British Journal of Cancer for consideration for publication and was finally accepted in April 1996. In April 1996, I started clinical work with Professor Michael Baum at the Royal Marsden Hospital. Between April 1996 to October 1996 the protocol for intra-operative radiotherapy was developed based on the pathological /biological rationale described in the BJC paper.

Photoelectron corporation agreed to sponsor a part of the Research fellow's salary to develop the machine and adapt it for treatment of breast cancer. As discussed in the chapter on technique, we developed the various applicators for use in the breast. There was considerable delay caused

by the Medical Devices Agency before these were approved for clinical use.

We proposed a long-term strategy for improving the local treatment of breast cancer in early 1997 as follows:

Long-term strategy for improving the delivery of local treatment for breast cancer

Pathological basis of localised radiotherapy.

Spatial distribution of dormant cancers in the breast

Clinical evidence of sites of local recurrence

The Hypothesis

Radiotherapy to the quadrant alone might be as good as radiotherapy to the whole breast in selected patients

The tools and methods for easier delivery of treatment

Intra operative radiotherapy

Interstitial stereotactic radiotherapy of small cancers

Establishing the efficacy and safety of the tools

Effect of interstitial radiotherapy in elderly women who would otherwise not undergo surgery. (Outcome measure: local control)

Effect of Intra-operative radiotherapy immediately after wide local excision as a substitute for the routine local boost. (Outcome measure: feasibility and local recurrence)

Planning randomised trials (multicentre and in India)

Early breast cancers: WLE + AD + localised RT vs. WLE + AD + Standard RT

Elderly women: Interstitial RT + Tam vs. Tam only

Small breast cancers including screen detected cancers: Interstitial RT only vs. standard Surgery + standard RT

Depending upon the results of the trials, application of the new techniques to benefit women world-wide

The ethical approval for the intra-operative boost radiotherapy project was given in October 1996. However, the medical devices agency (MDU) did not approve of the new device until June 1998.

During this period I tried to perform several experiments with Comet assay to evaluate the radiation dose and its effects at various distances. However, the dose from the PeC x-ray source fell off very quickly- so that the cells placed on a single microscope glass-slide received a differential dose. These were therefore not analysable using the Comet assay.

The first clinical trial using the PRS device was aimed to test its safety and feasibility and was commenced on 2 July 1998.

Background

Over the past 30 years, there has been a dramatic change in the local management of breast cancer from very radical to more conservative surgical operations, with the widespread use of radiotherapy in conjunction with wide local excision of the tumour itself. This shift away from radical surgery has been prompted by randomised clinical trials that have clearly demonstrated that conservative breast surgery followed by radiotherapy is equivalent to more radical procedures in overall survival [Early Breast Cancer Trialists' Collaborative Group, 1995]. However, although the outcome is 'conservative' the intention is 'radical' with the radiotherapy fields encompassing virtually all of the tissues previously excised by radical mastectomy. This approach needs to be reappraised. A component of the rationale for the less radical approach is that in large studies of breast conservative therapy more than 90% of early breast recurrences have been found to occur at the site of the original primary tumour. This is true whether or

not radiotherapy is given [Fisher et al., 1986] and whether or not the margins are involved [Vaidya and Baum, 1998]. Furthermore, this is the case in spite of the fact that, when mastectomy specimens are examined by detailed radiological-histological correlational methods, small additional invasive or *in situ* cancer foci are found in over 60% of patients, with 80% of these situated remote from the index quadrant. The relative distribution of primary tumour and these foci in the four breast quadrants is significantly different [Vaidya et al., 1996]. Hence it appears that these additional cancer foci do not in general give rise to local recurrence which more probably develops from the cells that surround the primary tumour. These may be overtly malignant or morphologically normal, yet capable of malignant progression, as evident by the loss of heterozygosity in these 'normal' cells within the index quadrant [Deng et al., 1996]. We have suggested that the next step is a clinical trial to test whether radiotherapy to the index quadrant alone can achieve as good a local control as radiotherapy to the whole breast [Baum et al., 1997] [Vaidya and Baum, 1998].

This approach of irradiating the index quadrant alone has been tested in two clinical trials and in fact (contrary to the

popular myth) the results of these trials are encouraging. The Christie Hospital Trial[[Ribeiro et al., 1993] randomised 708 patients to receive either the standard wide field (WF) radiotherapy or a limited field (LF) radiotherapy to the index quadrant. They found that overall there was a higher recurrence rate in the latter (LF) arm. In the limited field arm, a constant size of radiotherapy field was used, irrespective of the tumour size, and this could have resulted in several instances of 'geographical misses'. More importantly, when the results were analysed according to the type of the primary tumour, it was found that limited field radiotherapy was inadequate only in infiltrating lobular cancers or cancers with extensive intraductal component (EIC). In the 504 cases of infiltrating duct carcinoma, there was no significant difference in the local recurrence rates of the two arms. In the much smaller (n=27) Guy's Hospital Study[Fentiman et al., 1991] [Fentiman et al., 1996], a single continuous application of an iridium-192 implant delivering 55 Gy over 5-6 days replaced the standard radiotherapy regimen of whole breast radiotherapy plus tumour bed boost. The authors found a 20% increase in local recurrence compared to historical controls. However, as discussed in a letter in response to the study[Dale et al.,

1997], it was pointed out that the Biologically Effective Dose (BED) of the implant-only arm was 20% lower than the conventional radiotherapy arm and this almost completely explained the difference. In addition 12/27 patients in this study were node positive and 15/27 had involved margins - putting these patients at high risk of local recurrence anyway.

Methods and Design

We report here the pilot study approved by the University College London Hospitals Ethics Committee in which a novel method of radiotherapy is 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 novel technology is called the Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA and is now commercially available as Intrabeam.

The detailed technical details of the device and the operative technique have already been described in the preceding chapter.

Patients diagnosed using triple assessment (physical examination, imaging and cytology or histology), to have operable breast cancer and suitable for breast conserving surgery were recruited in the pilot study, after a full informed consent. In every case Dr Jeffrey Tobias, the consultant clinical oncologist, obtained the informed consent.

Each patient underwent wide local excision and axillary clearance. The details of the technique have been described in the preceding chapter. In the first 3 cases, the complete PRS device was sterilised. This required the Quality Assurance analysis to be done on the previous day before sterilisation and repetition in the operating theatre under sterile conditions. From the 4th case onwards, we wrapped up the XRS with sterile plastic bag, with a hole for the sterile applicator to pass through. Not only has this made the operation streamlined, it has also significantly reduced the time spent by the medical physics teams in the operation theatre. Since this modification, the average time needed to set-up the system at the end of excision was 12 minutes. When the lesion was on the left side, the chest wall was protected by thin polyurethane- tungsten impregnated sheets that could either be applied to the

applicator or custom-made to fit on the chest wall. This reduced the radiation by 99% and protected the heart and coronary vessels. The applicator sphere was inserted into the breast cavity and a deep surgical purse-string suture was inserted in the subcutaneous plane to bring together the target breast tissue so that it applies well to the surface of the PRS applicator sphere and holds it in place during radiotherapy, as described in detail in the preceding chapter. Our third patient had radionecrosis of the skin close to the scar, which we believe was the site of one of these subcutaneous stitches. Since then we have been retracting the skin with a 3-0 prolene stitch and ensuring that no part of skin is less than 1cm from the applicator surface. Essentially these 'conforming' stitches allowed hands-on-conformation of the target to the source of radiation. The radiation was switched on for 21 to 28 minutes depending upon the size of the applicator sphere, and using an energy of 50kV a dose of 5 Gray (Gy) was delivered at 1cm distance from the cavity margins. After completion of radiation, the 'conforming' stitches were removed and the skin was sutured in the usual manner with a subcuticular prolene stitch, which was left in place for 14 days.

The follow up of these patients was as usual with 3 monthly visits to the outpatients clinic and yearly mammograms. Any other investigations such as ultrasonography or fine needle aspiration cytology were performed if prompted by symptoms or signs.

We assessed the cosmetic results of the patients with photographs and by comparing patient's own assessment of the cosmetic result. We asked the patients to score the appearance and texture of the breast on an analogue scale of 1 to 10, 10 being the best. We also asked her at the same time, to give a similar score to what she would have expected the appearance and texture to be, again on an analogue scale of 1 to 10, 10 being the best. The satisfaction index was calculated by dividing the patient's score for the actual (observed) appearance (and texture) by her score for what she would have expected it to be (expected). We felt that ultimately, it is the patient's own assessment that is more accurate depiction of the 'real' cosmetic outcome. For comparison with other studies, the 'objective' assessment of photographs by an independent panel would of course be more relevant.

Results

We have completed 26 cases of intra-operative radiotherapy for breast cancer. The patients were diagnosed to have early operable breast cancer suitable for breast conserving surgery. The age ranged from 30 –80 years (Mean 51.5). The pathological tumour size ranged from 0.42 cm to 4.0 cm. The applicator size was 3.5 cm in 15 cases, 4cm and 3cm in 3 cases each, and 4.5 cm in 3 cases and 2.5 cm in 1 case. In all except the first case, the operating voltage was 50Kv @ 40microamperes. The time required to treat the prescribed dose of 5Gy at 1cm ranged from 21.1 min to 28.7 minutes. In the first case, we used a 40 kV voltage and took 36.8 minutes.

Three patients received intraoperative radiotherapy as the only form of radiotherapy. One patient was blind and 80 year old and not very suitable for daily postoperative visits for external boost radiotherapy. In a joint decision, she was prescribed 7.5 Gy at 1cm effectively giving about 23 Gy to the cavity margin as the only radiotherapy. Another patient had a contralateral breast cancer treated 14 years ago with interstitial wire boost and whole breast radiotherapy. In order not to overlap radiation beams in the sternal region,

she was prescribed 6 Gy at 1cm giving 20Gy to the cavity margin as the only radiotherapy. The third patient (Patient number 21 in the pilot study) was a lady who well understood the rationale of our subsequent randomised study and chose not to undergo the 5-wk course of whole breast radiotherapy, although we had not yet started the randomised trial to test this approach. All other patients received the routine external beam radiotherapy to the whole breast (50Gy over 5 wks, 25 fractions).

No patient has had major operative or postoperative complications, in general as well as regards the wound. Two patients had some problem with wound healing one of which we believe was due to excessive radiation and radionecrosis. This was our third patient as mentioned before, who had radionecrosis of an area of skin close the applicator. This resulted in delayed wound healing by secondary intention. After this case, we measured the skin dose using Thermoluminescent detectors (TLD). The mean of the highest dose of radiation at the skin surface was 4.6 Gy (95% CI 3.6 – 5.6, median 3.7). It has been between 5-10 Gy in 4 patients but has never reached about 10Gy. None of these 4 patients has had any complications.

In the 80-year-old blind lady, both the axillary and primary wound had delayed wound healing that was probably age related. One other patient had wound infection - but the wound healed satisfactorily within 2 weeks and did not delay her adjuvant treatment. Some non-tender transient erythema around the scar was seen in 3 patients.

The longest follow up is 45 months, with a median of 34 months and a minimum of 27 months. No patient has had a local recurrence. None of the patients whom we found suitable have refused to participate in the study. Many patients found the technique 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' also was very attractive.

The actual score of appearance of breast and texture of breast, as judged by the patients themselves, either matched or exceeded their expected score in 21 out of 25 patients. At 12-24 months after surgery, the satisfaction index (observed/expected score) was 1.2 (95% CI 1.1-1.4) for breast appearance, and 1.2 (95% CI 1.0- 1.4) for breast texture.

Discussion

In the present protocol, the PRS was used for boosting of the tumour bed in conjunction with external beam irradiation to the whole breast which provided a saving of 1 week of radiotherapy treatment time and travelling for the patient. In those patients undergoing sentinel node excision with immediate frozen section, intra-operative radiotherapy could actually be delivered during the time waiting for the frozen section results.

In addition, the PRS technique has advantages over other types of brachytherapy. At present, both low-dose-rate and high-dose-rate brachytherapy are employed in order to maximise local dosage for improved local control, but the techniques are time-consuming and expensive. Careful placement of semi-flexible I¹⁹² IR wires probably represents the "gold standard" brachytherapy technique at present but geometrical accuracy is important and the implant must be removed at a later date, increasing the workload and creating additional problems of radiation protection.

Intraoperative radiotherapy has been explored in the past, employing massive and expensive linear accelerators that required relocation of the operation theatre in the radiotherapy suite. Mobile linear accelerators are now being used by several groups in the world, most notably Professor Umberto Veronesi's group. The advantage of using the linear accelerator (e.g. NOVAC-7) high-energy electrons is that the actual treatment time is reduced to a few minutes. However, the positioning of the equipment takes much longer and the total time for treatment is about 25 to 35 minutes. Furthermore, the shape of the radiation is different from the one which we use – it is in the form of a radiation beam- so that the target tissue – the breast cavity - needs to be brought facing the radiation source. With the Intrabeam device, the radiation is delivered from within the breast, which intuitively appears a much more elegant approach.

Nevertheless, whichever technique is able to accurately and relatively inexpensively deliver radiotherapy to the target tissues in the operating theatre in a reasonable time would revolutionise the local management of breast cancer.

We believe we are the first to use this approach and the technique we use is simple, portable, and can be used in a

routine operation theatre. It provides a simple form of brachytherapy, which could potentially provide equivalent benefit with a lesser demand on professional time expended. We recognise that the follow up of this study is relatively short (median 34 months and longest 45 months) for assessing local recurrence rates, but this study was a pilot phase II study mainly testing the feasibility, safety and acceptability of the technique to the patient and not local control, which will be tested in the next phase- the randomised trial. Nevertheless, it is encouraging to have a 0% local recurrence rate at nearly 3 years of follow up.

Another important value of the pilot project is that it has demonstrated that it is safe, at least in the relatively short term, to deliver a very high dose of radiotherapy –the Intraoperative dose in one fraction followed by 50Gy of postoperative whole breast radiotherapy. The lack of side effects until now is probably due to the fact that the high dose is small and for the same reason, we expect that the late fibrosis, if any, will not be disfiguring.

This method of delivery of radiotherapy offers excellent radiation dosimetry and does not have the risk of a “geographical miss”. The treatment is delivered at the

earliest possible time after the surgery. It has been suggested that a large proportion of local recurrence after breast conserving therapy is because of a geographical miss of the boost dose. It has been estimated that the boost dose could miss between 24% to 88% of the target volume[Sedlmayer et al., 1996;Hunter et al., 1996;Krawczyk and Engel, 1999;Machtay et al., 1994]. Thus a large proportion of local recurrences could be attributed to geographical miss alone.

In patients with high risk of local recurrence (e.g. larger tumours with high nuclear grade and with involved nodes) this approach can offer the most optimal mode of delivery of radiotherapy, and may have the potential to reduce the local recurrence rate substantially.

It is the next phase, that we would test whether giving targeted localised radiotherapy in this manner is equivalent to the routine 6-weeks course of postoperative radiotherapy in selected patients; then this technique has a potential to save 6 weeks of external beam radiotherapy time for both the patient and the overstretched resources of radiotherapy departments.

We received ethics approval and have begun in March 2000, a randomised trial (called Targit- **Targeted Intraoperative Radiotherapy**) comparing conventional radiotherapy to radiotherapy delivered to the index quadrant alone using the PRS – this is described in the chapter 7.

Summary

Introduction: We believe that conservative treatment of breast cancer may not require radiotherapy that encompasses the whole breast. This chapter discusses the clinico-pathological basis for this view as well as a novel therapeutic approach that allows intra-operative radiotherapy to be safely and accurately delivered to the target tissues in a standard operating theatre. **The Rationale:** Whole-organ analysis of mastectomy specimens reveals that 80% of occult cancer foci are situated *remote* from the index quadrant. In contrast, over 90% of local recurrences after breast conservative therapy occur *near* the original tumour- even when radiotherapy is not given. Therefore, the remote occult cancer foci may be clinically irrelevant and radiotherapy to the index quadrant alone might be sufficient. **A Novel Technique** The Photon Radiosurgery System (PRS) is an ingenious portable electron-beam driven device that can typically deliver, intra-operative doses of 5 - 20 Gy, respectively, to 1cm and 0.2cm from the tumour bed over about 22 minutes. The pliable breast tissue - the target - wraps around the source providing optimal conformal radiotherapy. Being soft x-rays,

the dose attenuates rapidly ($\alpha \sim 1/r^3$), reducing distant damage. **Results** In our pilot study of 26 patients (age 30-80 years, T=0.42-4 cm), we replaced the routine post-operative tumour bed boost with *targeted intra-operative* radiotherapy. There have been no major complications and no patient has developed local recurrence although the median follow-up time is short 34 months. **Conclusion** It is safe and feasible to deliver *targeted intra-operative* radiotherapy (*Targit*) for early breast cancer. This novel method of delivery of radiotherapy, used alone, could be used in a randomised trial testing the hypothesis that index quadrant irradiation alone may be adequate local treatment for selected cases of breast cancer. In other patients, in whom whole breast irradiation is deemed necessary, this method can be used to accurately deliver the tumour bed boost at a high therapeutic ratio, without the risk of a geographical miss, with a potential to reduce the overall local recurrence rate.

CHAPTER 6

Percutaneous minimally invasive Stereotactic Interstitial primary radiotherapy using the Photon Radiosurgery System for women found unfit to undergo surgery

Background

There is a relatively large group of women with breast cancer in the elderly age group who have significant co-morbid conditions that raise the risk of operative intervention. This group of elderly women can contribute to more than half of all breast cancers diagnosed in an ageing population[Yancik et al., 2001]. Since a high proportion of these tumours are oestrogen receptor positive, the traditional treatment of these women has been oral tamoxifen alone. There have been three randomised trials testing whether local treatment is beneficial for elderly women with breast cancer. In the Nottingham trial, [Robertson et al., 1992], 135 consecutive patients aged over 70 years with operable primary breast cancer (< 5 cm) were randomised to either wedge mastectomy or tamoxifen 20 mg twice daily as initial therapy. At a mean follow up of 65 months, there was no difference between the two groups in terms of overall survival or cause of death. However, failure of locoregional control was significantly greater in the tamoxifen group. The authors concluded that optimum treatment for elderly patients with

operable breast cancer should include mastectomy. In the trial from St George's Hospital, London[Gazet et al., 1994] conducted between 1982 and 1989, 200 patients aged 70 or over seen in one Breast Unit, who were considered to have a surgically resectable cancer of the breast were prospectively randomized to primary surgery or tamoxifen 20 mg per day. At a median follow-up of 6 years (range 3-11 years), there were 61 events in the tamoxifen arm while and 50 events in the surgical arm. There were 33 deaths in the tamoxifen group and 28 deaths in the surgical group of which 17 and 15, respectively were directly attributable to breast cancer. The disease-free interval did not differ between the two groups. In the tamoxifen group, 39 had no progression of their disease and a further 21 benefited from subsequent surgery. In the surgical group 50 had no recurrence of their disease and a further 10 benefited from subsequent tamoxifen therapy. Thus surgery, offered the most time free from disease.

The largest trial to address this issue is the recently concluded CRC clinical trial [Latteier et al., 1997;Bates T, 2001;Bates et al., 1991;Latteier et al., 1997]. They prospectively randomised 450 women over 70 years of age with operable breast cancer to receive either tamoxifen 40

mg per day, or the same dose of tamoxifen plus breast surgery. In this pragmatic trial, the extent of surgery was not prescribed. Overall, there were 149 deaths among the 220 women receiving surgery-plus-tamoxifen, compared 120 deaths among with 230 women receiving tamoxifen alone (RR=0.82, 95% CI 0.64- 1.04). However, when breast cancer deaths were considered, there were 36 in the surgery arm compared with 61 in the tamoxifen-only arm (RR =0.62, 95%CI 0.41-0.94). Of those who received tamoxifen only, 34% achieved complete response (CR), 11% partial response (PR), and 38% remained stable. Median response durations were 38 months (CR) and 14 months (PR) and 33 months (stable). Ninety-one women (40%) in the tamoxifen-only group had subsequent breast surgery. Survival of those with delayed surgery was no worse than for those in the primary treatment arm (RR =1.16 95%CI 0.85-1.60).

These results suggest an effect of early local treatment, in the form of surgery, had an effect on overall and cancer specific survival. Thus the local treatment of breast cancer in this age group should be given high priority. However, many of these women are frail and surgical treatment is not applicable because of co-morbid conditions. If the patient is

not fit enough to withstand surgery, some form of effective local treatment can be reasonably assumed to be of benefit. As discussed earlier, we believe that this local treatment many not need to involve anything more than treatment of the index quadrant of the breast. We piloted the use of the PRS system, using the bare probe alone in this group of women, using novel minimal intervention therapy incorporating three converging technologies: a - the Fisher Mammotest table for digital real-time tumour localisation b- the Mammotome Vacuum biopsy system for excision biopsy and c- the PRS400(PeC) for localised portable radiotherapy.

The Physics

The dose of radiotherapy at the tip of the XRS is very high. The difference between these treatments and those that we piloted for intra-operative use was that in these women the tumour was not excised. Thus, while planning radiotherapy dosimetry we calculated a dose of 5 Gy at 1cm from the surface of the tumour, so that the effective area of normal breast tissue that would be radiated would be similar to that in the intra-operative study while the tumour itself received a very high dose of a single dose of radiotherapy

in a small volume. Typically, the physical dose at the centre of the tumour is about 135 Gy.

While planning the dosimetry for this pilot, we modelled the dose as if the nearly spherical tumour was the applicator that we used for intra-operative radiotherapy, so that the dose at 1cm from the tumour surface was similar to that received by normal breast tissue after surgical excision. Thus the prescribed dose was 5Gy at 1cm from the tumour surface. This usually allowed the treatment to be delivered in 6-12 minutes for tumours ranging from 1cm to 3cm in diameter.

The Technique

A Fisher Mammotest prone table uses two digital mammographic images 30° apart to stereotactically compute the location of lesions in the breast. The intervention devices are mechanically compatible with the system. Thus, the Mammotome vacuum biopsy apparatus and the PRS400 X-ray source can be mounted on the calibrated stand and can be directed to the correct location within the breast with real-time monitoring.

The patient lies prone while the breast is suspended under the table between the image sensor and a small windowed

compressing pad. The Mammotome vacuum biopsy apparatus is targeted at the lesion through a tiny incision in the breast following local anaesthesia. Using this equipment, it is usually possible to take about 1-2 cm³ of tissue. This is adequate for tissue diagnosis, can be therapeutic for benign lesions and may achieve near complete excision for small screen detected malignant lesions[Beck et al., 2000]. PRS400 (PeC) is an electron-beam driven soft x-ray source, which provides a point source of low energy X-rays at the tip of a 3.2mm diameter tube that can be positioned in the breast through the tract created by the Mammotome needle. With a 50kV machine, the typical dose is about 130Gy and 20 Gy at the surface of the tumour delivered in 8- 12 minutes in a routine x-ray room. With this approach, the area of maximum tissue anoxia - the most likely site of failure receives the highest dose and the normal tissues receive the least.

The X-ray source is not sterilised. A sterile thin transparent plastic, relatively stiff tube with a flange at the base - that slides smoothly over the 3.2mm bare probe is used. These tubes are pre-sterilised in disposable packs. It does not interfere with the radiation dose. It is slid onto the probe just before it is inserted into the breast as described below.

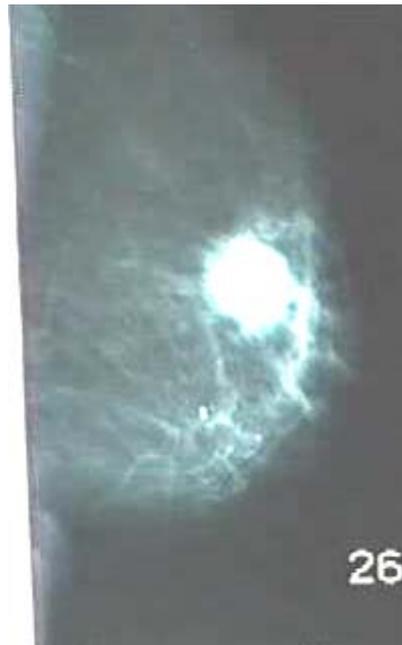
After diagnosis of the carcinoma, usually in a previous outpatient visit, by triple assessment, patients were invited to take part in the trial. Once informed consent was obtained the procedure was performed in the radiology department in a morning session, on an outpatient basis.

Ethics approval for this study included the permission to withhold tamoxifen for 1 month after treatment, following which it was started at 20mg per day. We assessed the response to radiotherapy using serial contrast-enhanced MRI scans of the breast, pre-operatively, at 6 days, at 1 month and at 6 months. In this way, the scans until 1 month were able to give an indication of the response of the tumour to only the radiotherapy.

The patients received the radiotherapy on the MammoTest machine. MRI was performed before and on at various periods after the radiotherapy was completed. Tamoxifen was started after 1 month.

Description of the first case.

A 73 year old lady presented with a lump in her breast. Clinically, it was a 2.5 cm tumour in the upper outer



quadrant, with no palpable axillary lymphadenopathy. Ultrasonography and mammography revealed a 2.5 cm tumour and fine needle aspiration confirmed a duct carcinoma. Several months ago, she was diagnosed to have motor neurone disease, confirmed on MRI, causing pseudobulbar palsy, the main symptom being slurring of speech. She could not therefore be offered surgery, although it has been shown to be beneficial, in addition to systemic tamoxifen.

After a full informed consent, she underwent, Mammotome

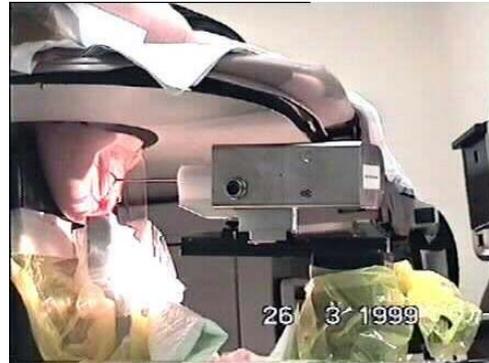


Mammotome biopsy in progress



vacuum biopsy followed by localised radiotherapy for this tumour using the Photon Radiosurgery System (PRS) on the Fisher Mammotest prone table. Following radiotherapy we excised two more cycles of core biopsies using the Mammotome in an attempt to partially excise the tumour.

During the whole procedure, the patient was prone on the table, which has a window for the relevant breast. The



PRS400 device in position



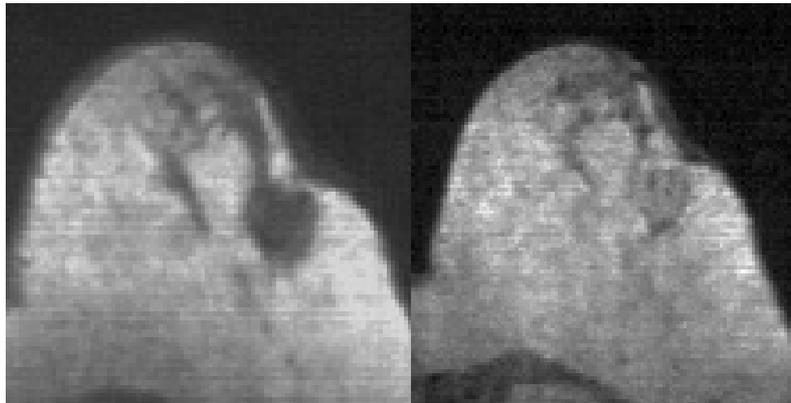
breast was then suspended between the image sensor and a small windowed compressing pad, under the table. The Mammotome vacuum biopsy apparatus is mounted on the calibrated stand and was directed to the correct location through a tiny incision on the breast under local anaesthetic. The position of the tip of the Mammotome needle was ascertained in real time by taking two stereotactic digital mammography images.

In this case, the Mammotome was used as above to make a tract and take 2 core biopsies from the centre of the tumour. The Mammotome was then removed from the breast, while keeping the breast in its position.

The bare probe of the PRS X-ray source was then covered with a sterile transparent plastic sheath. The PRS was now mounted on the stand and the tip stereotactically directed to the centre of the tumour in the breast. The position of the tip was again ascertained in real time to be in the centre of the tumour and then the radiotherapy was started. During the radiotherapy, the radiographer remained in the room behind a shield. Over 12 minutes, the tumour received a varying dose, from 134 Gy at the centre to 23.5 Gy at the surface. The closed skin was at 2.5 mm received 16 Gy. The whole procedure was completed in 50 minutes.

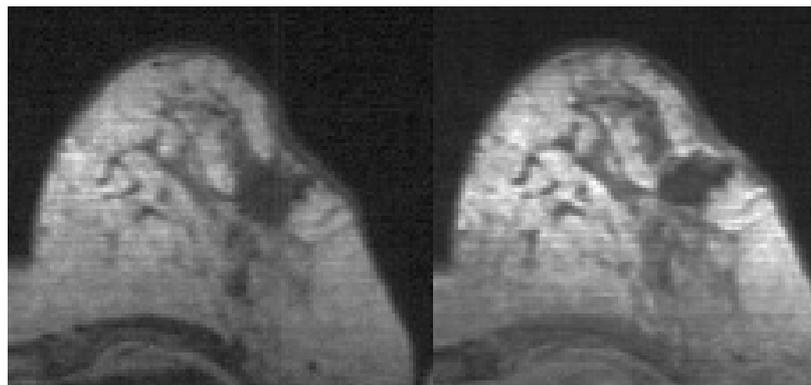
These are the early MRI pictures that demonstrate, apart from a small area in the periphery, a very promising near complete absence of enhancement in the post- treatment image of the tumour.

MRI- Before Treatment



Pre-contrast.....Post-contrast

6 days after Treatment



Pre ContrastPost-contrast

Clinically, the skin looked normal and the patient suffered no pain, bruise or any discomfort at all. MRI at 4 weeks and at 6 months revealed that even this marginal enhancement had gone away. Core cut biopsies taken at the time of the MRI, 1wk and 4wks after the radiotherapy treatment, showed progressive evidence of apoptosis, necrosis and fibrosis. The tumour was impalpable at 3 months. At the

last follow up visit 12 months after the treatment, the patient was disease free as regards breast cancer, but her neurological condition had deteriorated considerably and she died at 13 months.

Results and Discussion

As a demonstration of principle, we have treated 3 patients with symptomatic breast cancer aged 73, 78, and 85 years. The aim was to partially resect the tumour and develop a track for the radiotherapy probe. The main treatment modality was intended to be radiotherapy. These patients had considerable co-morbid conditions- partial pseudobulbar palsy in the first and cardiac dysfunction in the other two. The cytological diagnosis of cancer was established a preceding outpatient visit. The tumour size was 2.5cm, 3cm and 2.8cm. All patients tolerated the procedure well.

The tumour samples taken by Mammotome after radiotherapy revealed histological evidence of coagulative necrosis and radiotherapy damage. In every patient, there was near complete loss of tumour vascularity on contrast-enhanced MRI within 6 days of treatment, apart from a thin rim of enhancement, which disappeared in the follow up

scans at 1, 3 and 6 months. All lumps were impalpable by 3 months and the patients were disease free at 13, 18 and 12 months following treatment.

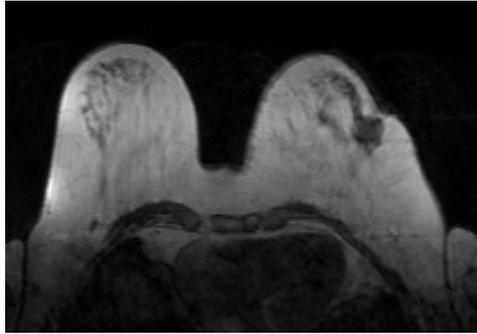
Two patients (1st and 3rd) succumbed to their co-morbid conditions, and thus did not suffer consequences of the breast cancer. The second patient remains recurrence free. The combination of these three evolving technologies can yield the diagnosis, localisation, part excision and radiotherapy in a single session under local anaesthetic in these frail women. The application with the biggest therapeutic potential is possibly the treatment of small screen detected cancers, in whom standard surgery and radiotherapy may represent over-treatment.

The MR Images and histopathological slides at various times are shown in following pages.

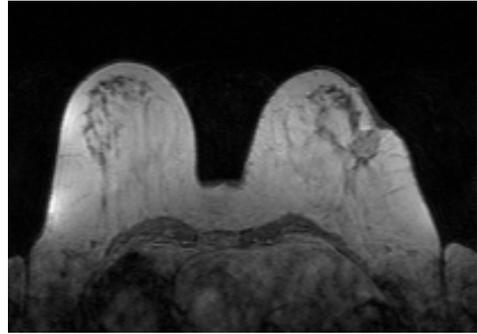
Case 1

25 March 1999 Pre treatment

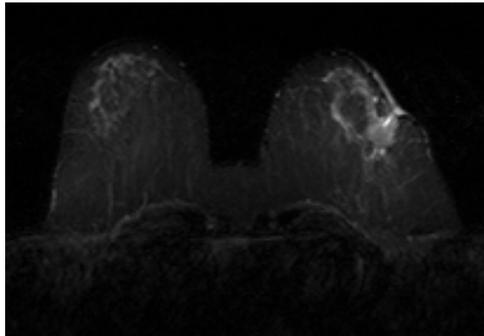
Pre-contrast



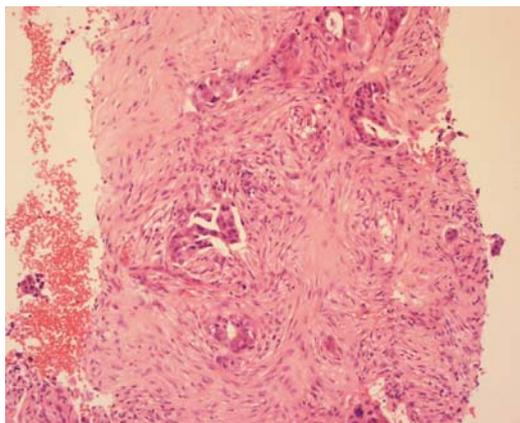
Post-contrast



Subtraction image



Core biopsy: Invasive duct carcinoma

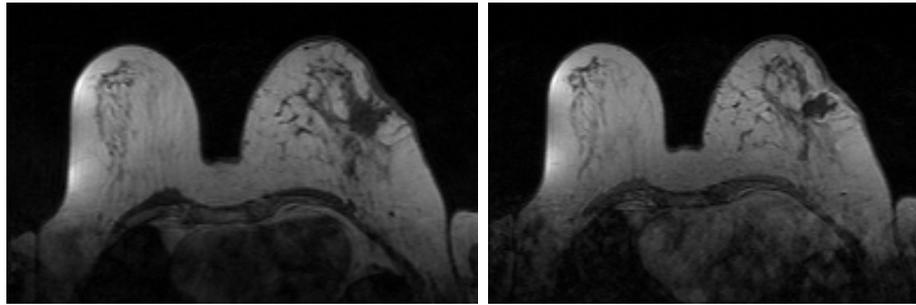


26 Mar 1999- PRS treatment

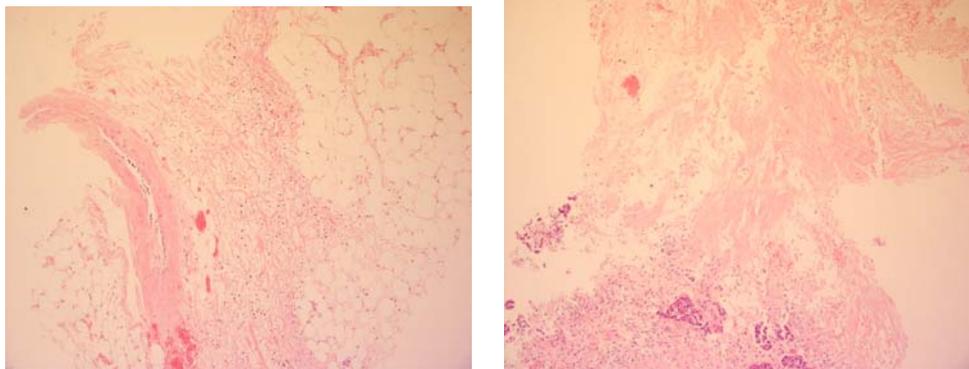
1 Apr 1999: 6 days post treatment

Pre contrast

Post contrast

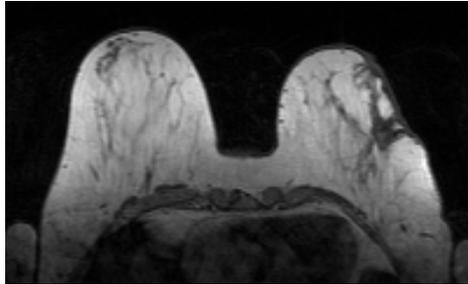


Histology – fibrosis and dying tumour cells

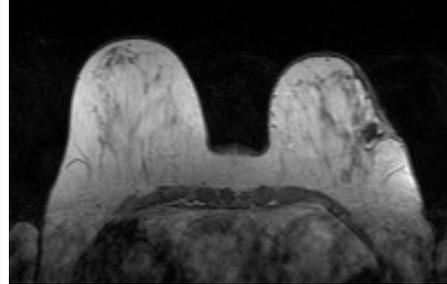


21 April 1999 - 4 weeks

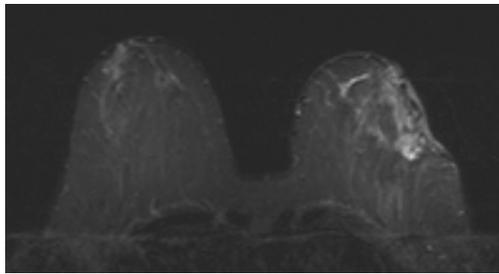
Pre contrast



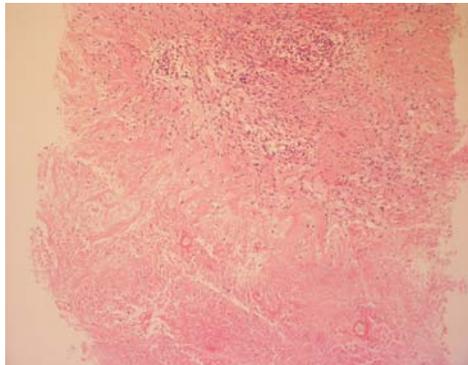
Post contrast



Subtraction

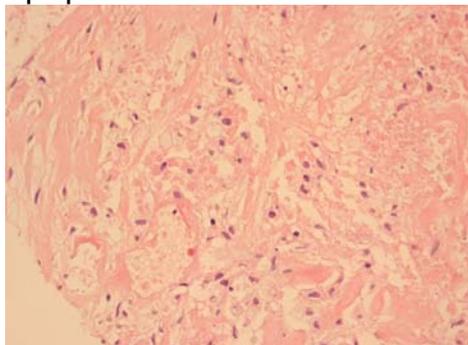


Histology: progressive fibrosis



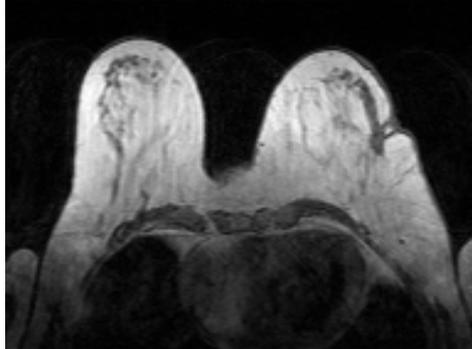
occluded vessels

apoptotic cells

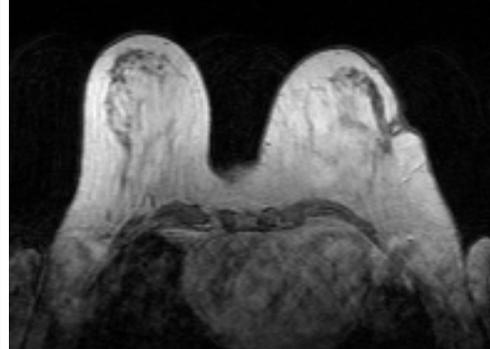


23 June 1999 (3 months)

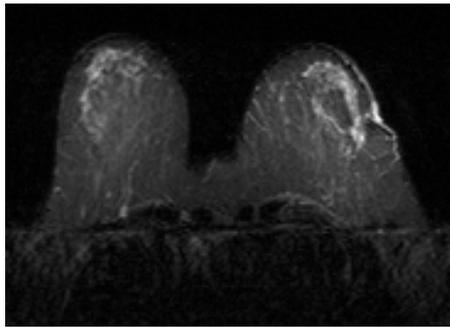
Pre contrast



Post contrast



Subtraction



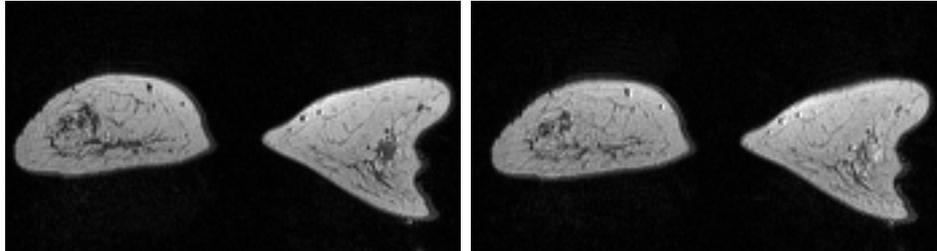
No Palpable tumour- no biopsy taken

Case 2

22 Sep 99 **Pre treatment**

Pre contrast

Post contrast



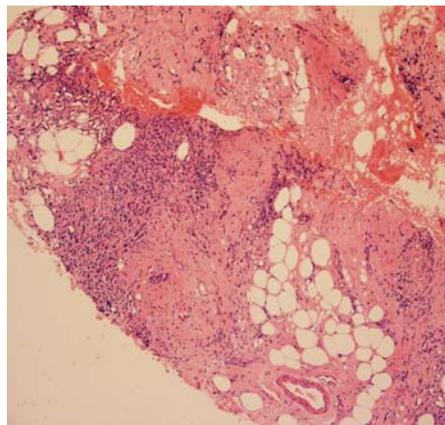
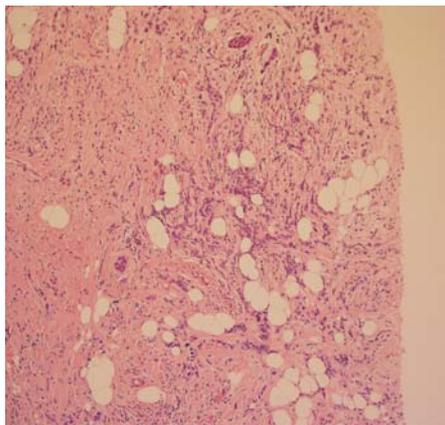
8 October 1999 PRS Treatment

Histology

Pre treatment

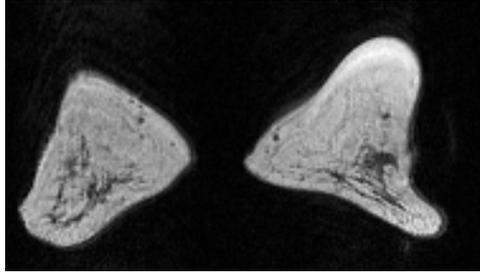
&

15 min after treatment

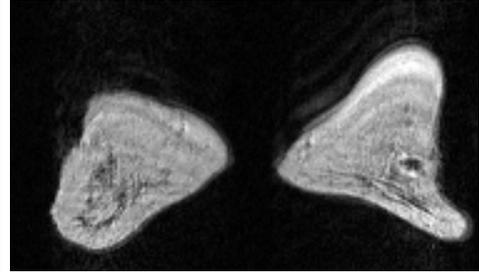


20 October 1999 (12 days)

Pre contrast

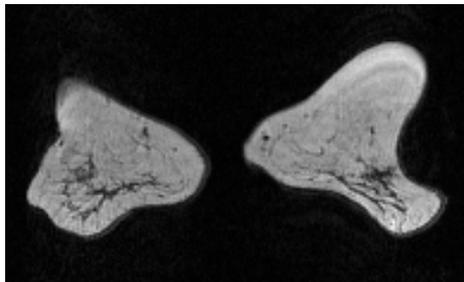


Post contrast

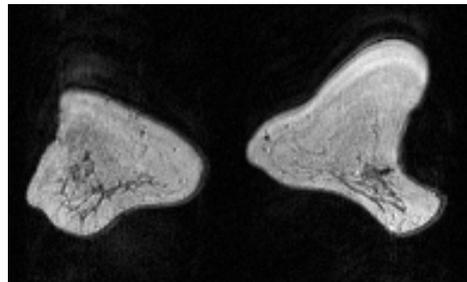


12 Apr 2000-(6 months)

Pre contrast



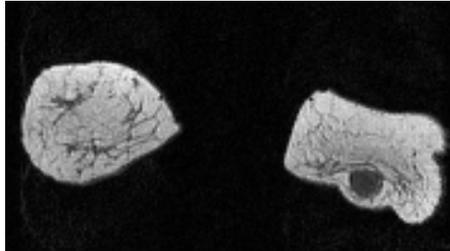
Post contrast



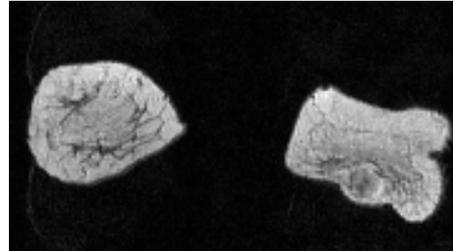
Case 3

2 Dec 1999 Pre treatment

Pre contrast



Post contrast

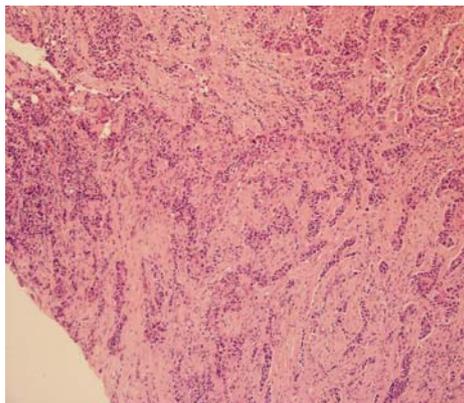


3 Dec 1999 PRS Treatment

Histology

Pre treatment

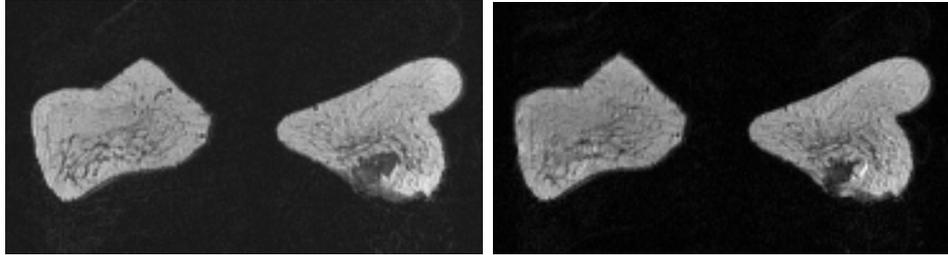
15 min after radiotherapy



15 Dec 1999 (12 days)

Pre contrast

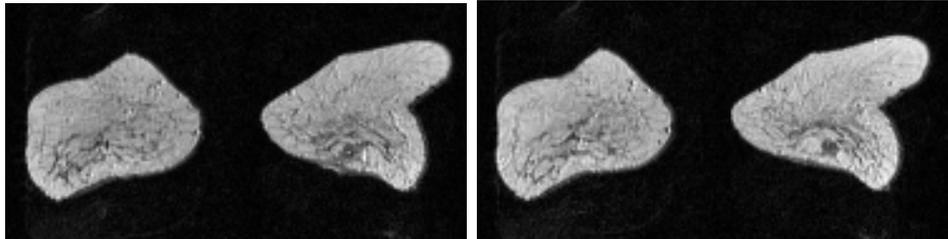
Post contrast



12 February 2000 (2 mon)

Pre contrast

Post contrast



CHAPTER 7

The randomised trial of targeted intraoperative radiotherapy

The problem of local treatment of breast cancer

Although there is strong evidence for the effectiveness and safety of breast conserving therapy (BCT) a large proportion of women still undergo mastectomy. In a sample of over 16000 women treated for Stage I and II breast cancer North-eastern America in 1994, breast-conserving therapy was performed in only 42.6% of patients[Morrow et al., 2001]. Apart from having T1 and EIC- negative tumours, the main predictor of undergoing BCT. Women over 70 were less likely to receive radiation and overall only 86% of patients who underwent BCT received radiation therapy. Many women in India frequently choose mastectomy because they cannot live or travel every day to the metropolis like Mumbai or Delhi to receive the 6 weeks of postoperative radiotherapy. This is not limited to developing countries alone. Similar dilemmas are faced by women in remote areas of the developed world as well. The inverse relationship of travel distance to radiotherapy centre and receipt of breast conserving therapy has been documented in Australia[Craft et al., 1997] and the USA[Athas et al., 2000;Nattinger et al., 2001]. In the large US[Nattinger et al., 2001] study using SEER dataset, living

between 15-20 miles away from the radiotherapy facility reduced the odds of receiving breast conserving surgery (BCS) from 1 to 0.76 and if the distance was more than 40 miles, it reduced the odds of receiving radiotherapy after BCS from 1 to 0.55. When the travel distance was <10 miles, 82% of patients received radiotherapy after BCS; when it was 50-75 miles, 69% received it and when it was ≥ 100 miles, only 14% received it. These patients accounted for 39%, 22% and 14%, respectively, of those would have been eligible for BCS + radiotherapy[Athas et al., 2000].

In the countries where the health system is delivered by the State, e.g., the UK National Health System, there are long waiting lists for postoperative radiotherapy. Overall, breast cancer contributes almost a third of patients to the radiotherapy units and any measure to free up radiotherapy resources would be welcome.

The rationale of a change in strategy for local treatment of early breast cancer is described in the earlier chapters of this thesis. In short, it appears that the symptomatic cancer usually restricts itself to the original quadrant in the breast.

Despite finding many other widely scattered small occult or dormant cancers in the diseased breast, it appears that these do not usually give rise to local recurrence. Local recurrence occurs at the site of the original primary tumour site in more than 90% of cases. Surprisingly, this is true whether or not radiotherapy is given and whether or not margins of the primary excision are involved. Various theories to explain this phenomenon have been discussed. Whether we can explain this satisfactorily or not, the practical consideration is that local recurrence probably arises either from or within the cells surrounding the primary tumour. Hence this should be the target of our therapies. The clinical implication of all these studies was that it is perhaps effective to only treat the index quadrant of the breast. Surgical excision of the whole index quadrant can result in recurrence rate equal to that achieved by wide local excision and radiotherapy [Veronesi et al., 1993]. However, quadrantectomy can be very disfiguring and 20-30% of patients are not satisfied with the outcome [Amichetti et al., 1995]. Substituting the large quadrant surgery by using lumpectomy and local field external radiotherapy has been tested against the usual wide field radiotherapy in the Manchester-Christie hospital trial, as

discussed in the previous chapter. The cosmetic outcome of this type of external local field radiotherapy was also very poor, leading the abandoning of this approach.

We have pioneered the use of a novel therapeutic advance in radiotherapy technology for breast cancer. We have piloted the technique as described earlier and found it safe and feasible in a routine operating theatre[Vaidya et al., 2001].

The current on-going clinical trial will test whether radiotherapy to the index quadrant alone can achieve as good a local control as radiotherapy to the whole breast. This approach has been tested in the Christie Hospital Trial mentioned earlier. In this trial although the cosmetic outcome was poor, the local control was equal in the two arms- i.e., localised radiotherapy was adequate for patients with infiltrating duct carcinoma, but not for patients with infiltrating lobular cancers or cancers with extensive intraductal component (EIC). In the current trial, these latter patients will receive whole breast radiotherapy.

Recent evidence, available after this thesis was drafted, suggests that index quadrant radiotherapy alone is in indeed effective when used in selected patients. Several

groups have published pilot studies and one randomised trial is in press. When patients with small infiltrating duct cancers with uninvolved nodes are treated with interstitial brachytherapy with radioactive wires, the recurrence rate is between 0% and 4% at 2-5 year follow up (see table)

Institution	Radio-therapy technique	Median follow up	Crude local recurrence rate (actual numbers)
Ninewells Hosp, Dundee, UK [Samuel et al., 1999]	LDR	5.6	0% (0/11)
Ochsner Clinic, USA [King et al., 2000]	LDR/HDR	3.8	1.3% (2/150)
London Regional Cancer Centre, Canada [Perera et al., 1997]	HDR	1.7	2.6% (1/39)
William Beaumont Hospital, USA [Vicini et al., 2001]	LDR/HDR	3	0% (0/174)
Orebro Medical Centre, Sweden [Samuel et al., 1999;Johansson et al., 2000]	PDR	2.8	2.3% (1/43)
University of Kansas, USA [Krishnan et al., 2001]	LDR	4	0% (0/24)
National Institute of Oncology Hungary [Polgar et al., 2000]	HDR	4.5	4.4% (2/45)
National Institute of Oncology Hungary[Polgar et al., 2000]	HDR/EBRT	2	0% (0/78)
Tufts University, USA [Wazer et al., 2001]	HDR	2	0% (0/30)
European School of Oncology, Milan, Italy [Veronesi et al., 2001]	IORT	<1	0% (0/84)

LDR=low dose rate; HDR=high dose rate; PDR=pulsed dose rate; IORT=intraoperative (electrons) radiotherapy;

Methods and Design

Targit is a randomised trial to test whether a single fraction of radiotherapy delivered intra-operatively and targeted to the tissues at the highest risk of local recurrence is equivalent to standard 6-weeks' postoperative radiotherapy

after breast conserving surgery in selected patients with early stage breast cancer who are suitable for breast conserving surgery. The major endpoint is local recurrence rate but in addition cosmesis, patient satisfaction and health economics will be assessed.

If this single dose of intraoperative radiotherapy is proven to be equivalent to the standard 6 weeks postoperative radiotherapy, the implications are obvious. It will save money and effort for the health service and for the patients. In addition, many women from the developing world will be able to avail of breast conserving surgery, instead of having a mastectomy just because they do not live near a radiotherapy centre.

This trial has been approved by the University College Hospitals Ethics Committee (99/0307) and we have begun accrual on 29 March 2000. We have randomised 29 patients to date (June 2001).

Title of the trial

TARGIT- TARGETed Intraoperative radioTherapy vs. Post-operative radiotherapy :A randomised controlled trial to compare targeted intra-operative radiotherapy with

conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer

Hypothesis

Strategy 1 (Target) – All patients will receive targeted intraoperative radiotherapy. If the histopathological analysis shows any of the following features suggesting high risk of local recurrence elsewhere in the breast (lobular carcinoma, or extensive intraductal component (EIC>25%)), they will also receive whole breast external beam irradiation.

Strategy 2 (control) – All patients receive whole breast external beam irradiation including conventional tumour bed boost.

The hypothesis is that Strategy 1 and Strategy 2 are equivalent.

Eligible patients

- All patients aged 18 years and above (some centres may decide at outset to recruit only women above 40 or even 65 years of age)
- Operable breast cancer (T 1-3, N0-1, M0) suitable for breast conserving surgery

- Cytological or histological confirmation of carcinoma
- Contralateral breast cancer in the past – these patients will be randomised to a separate stratum.

Exclusion criteria

- More than one obvious cancer in the same breast as diagnosed by clinical examination, mammography or ultrasonography.
- Bilateral breast cancer at the time of diagnosis
- Patients undergoing primary medical treatment as initial treatment of invasive breast cancer
- Histological diagnosis of invasive lobular carcinoma or EIC
- Confirmed deleterious mutation in the BRCA1 or BRCA 2 genes. These patients appear to have an extremely high (nearly 50%) risk of local relapse in a conserved breast [Haffty et al., 2002]

End Points

Local tumour control (defined as recurrent tumour in the ipsilateral breast)

Patients will be regularly monitored as per the individual centre's policy provided this meets the minimum criteria for

follow-up of symptomatic breast cancer patients as defined by the Breast Specialty Group of the British Association of Surgical Oncology. Confirmation of recurrence will follow clinical examination and cytology or biopsy.

Cosmetic result

Photographic assessment by a physician and breast care nurse not participating in the trial will be performed at 2 years. The assessors will be kept ignorant as to which of the treatments any particular patient received. Photographs will be assessed for cosmetic outcome and normal tissue damage using a standardised rating scale.

Patient satisfaction

About delivery of treatment and the acceptability of the cosmetic result will be elicited at 6 weeks and at 2-3 months (for those not receiving chemotherapy) or at 8-9 months (for those receiving chemotherapy) and at similar times after the completion of postoperative radiotherapy for those in the control arm.

Patients will be requested to fill in a diary during postoperative radiotherapy and at a corresponding time in the IORT arm. Apart from the time that is spent to attend

the daily sessions of radiotherapy, it will also record the feeling of tiredness and hindrance to daily work on a score of 0-3

Health economics

A protocol to evaluate the cost of the new treatment in comparison to standard breast irradiation will be developed in the feasibility stage of the trial.

Trial Schema



*May 2002 modification e.g., patients less than 45yrs, pT>2 cm, pN positive, grade 3, ER negative. This is subsequent modification of the protocol.

Treatment Policy Statements

Only clinical centres with the Photon Radiosurgery System or who are able to refer patients to such a centre may enter patients to the trial. Prior to entry of any patients each centre will register with the trials office and complete a Policy Statement which will define the categories of patients to be entered (e.g. some centres may elect only to enter older women) and some details of treatment policy (e.g. fractionation and dose of conventional radiotherapy to be used). Any change to practice during the course of the trial must be notified to the trials office in writing prior to implementation. This is to enable the trials office to audit patients entered and treatment received.

Centres with newly acquired equipment must consult the principle clinical investigator at University College Hospitals prior to entering patients into the trial.

Treatments

Surgery

All patients will have local excision of the primary tumour following appropriate clinical work-up but no special assessments prior to randomisation will be required. Surgery will be according to usual local practice but at least Level II axillary node dissection must be performed unless protocols for sentinel node excision are being followed. Similar surgical technique must be employed in all patients regardless of the randomisation. It is impractical to blind the surgeon to whether the patient will be receiving intra-operative radiotherapy. However, in a pragmatic trial, it is the package that is being tested- and if it transpires that wide local excision and targeted intraoperative radiotherapy is effective, without compromising cosmetic outcome, then it does not really matter that a slightly wider excision was performed by the surgeon. The wideness of excision will be assessed prospectively using the ratio of tumour size and specimen weight as an indicator.

Radiotherapy

Intra-operative radiotherapy will be delivered in the operating theatre immediately after the operative procedure. The dose of the intra-operative radiotherapy will be prescribed as 5 Gy physical dose at 1cm from the applicator surface.

Planning protocols for the conventional radiotherapy will vary from centre to centre but for each centre a written policy will be required. All patients randomised to receive conventional radiotherapy within this trial to should be treated in accordance with this policy. Dosage should only be applied to the chest wall – axillary, supra-clavicular and internal mammary nodes should not be irradiated by discrete fields. Patients with previously irradiated adjacent fields for example, those with previous contra-lateral breast cancer, will need to have the radiotherapy fields modified according to local policies.

Patients with Lobular cancer and Extensive Intraduct Component

Patients found on pathological examination of the operation specimen to have either invasive lobular cancer or

extensive intra-duct component will receive external beam radiotherapy since these patients are at a higher risk of developing recurrence in the ipsilateral breast at a site other than that of the excised primary. For those patients randomised to intra-operative radiation this will be in addition to the treatment they have already received.

The issue of positive margins

In the pilot study we only had one patient with positive margin- which was the deep margin. Since this was the blind lady who had received the higher (7.5Gy at 1cm) dose of radiotherapy, the area adjacent to the tumour bed would have received about 23Gy which was thought to be adequate therapy and a decision to give no further treatment was taken jointly in the multidisciplinary meeting and with the patient. In the randomised trial, the policy is to re-excise those patients with grossly positive margins and re-radiating the new 'correct' tumour bed if they were randomised to the intra-operative radiotherapy arm. Previous IORT should not contra-indicate this because the previously radiated area would have been excised in the re-excision.

Adjuvant Systemic Therapy

Following completion of randomised therapy patients may be recommended appropriate adjuvant therapy according to local practice or trial protocols. The policy for such treatments will be declared in the Policy Statement.

Trial Administration

Randomisation and data management of the trial will be carried out at the CRC and UCL Cancer Trials Centre. Clinical queries should be addressed to the Principle Investigator. A Working Party comprised of clinicians, a physicist, a statistician and the trial co-ordinator will regularly review the progress of the trial and address any problems.

Data Monitoring Committee (DMC)

An independent DMC will be appointed (or that constituted for the CRC Breast Cancer Trials Group will be used with the agreement of the Working Party). They will review the data collected during the feasibility trial and recommend whether the full study should be implemented.

Subsequent meetings will be scheduled at their direction but these are likely to be annually for the first two years of the trial whilst accrual gains momentum. More frequent meetings may be held at their or the Working Parties request.

There are no formal stopping rules for the trial – these may be determined in discussion with the DMC but should a difference between the treatments in local recurrence reach $p < 0.001$ serious consideration to continuation will be given.

Randomisation

When we first applied for ethics approval, we had proposed that the randomisation be done according to the Zelen Method.

The UCL ethics committee did not approve of this as a matter of general principle and we have used the standard randomisation procedure for the trial. Fortunately, as discussed later, we do not feel that this has reduced the patient accrual. However, it is important to note down the arguments for this case- for it may be required to be done in other centres as given in the next 4 paragraphs.

Then numbers needed for the same power with standard randomisation are smaller.

Patient entry into trial

Patients will be randomised prior to surgery but only after being informed of the trial and given written information. Every patient deemed suitable for the trial will be entered into the randomisation procedure once informed consent has been gained.”

Statistical Considerations

Patient Numbers and Power Calculations

The CRC Trial comparing the outcome for patients with good prognosis early breast cancer demonstrated a local recurrence rate of 9% at five years in the arm treated with conventional radiotherapy. The objective of the trial is to determine whether the use of intra-operative radiotherapy gives equivalent rates of local control to those obtained using external beam treatment. We define equivalence as ruling out a hazard ratio of greater than 1.5 (i.e. a change in recurrence rate from 9% to 13.5%). Since the use of the new technique would employ less resource this small

increase in absolute rate is deemed acceptable. Thus, equivalence will be concluded if the upper limit of the 2-sided 90% confidence interval for the hazard ratio does not exceed 1.5. Given the recurrence rates above, we could expect at five years about 75 events from about 850 patients entered per arm. If the population hazard ratio is one then the expected 90% confidence interval will be (0.7, 1.31).

Therefore to demonstrate equivalence with 90% confidence intervals the observed log hazard must fall below $[\log(1.5) - 0.269 = 0.137]$. The probability that this will occur when the true hazard ratio is one is 80% (i.e. the trial will have the power to demonstrate equivalence with 80% power with 833 patients per arm if the treatments are truly identical).

Recent modification of trial design

During the 3rd European Breast Cancer Conference at Barcelona in March 2002, several investigators from Australia, Europe and USA met to discuss the multicentre participation in the *Targit* trial. It appeared that most investigators would find it safer and wiser to restrict entry to those patients who are at lower risk of local recurrence. These patients would firstly be a subset of patients suitable

for breast conserving surgery and secondly have a low local recurrence rate in the range of 2-4%. In order to run an equivalence trial among these patients the sample size would need to be between 6000-8000 patients, making the trial rather impractical. It was suggested by the author that we should rather flip the trial over. Instead of setting up the trial to prove EQUIVALENCE of *Targit* and conventional 6-wks postoperative radiotherapy, we should set it up to prove a DIFFERENCE between two strategies (not treatments).

This is because we can expect that *Targit* will *reduce* local recurrence rates if given in addition to external beam radiotherapy in patients with high risk of local recurrence because of higher local dose, better biologically effective dosimetry and no geographical misses. At the same time, we can expect that in the low-risk group receiving *Targit* to have a local recurrence rate equivalent to conventional postoperative radiotherapy (<1% change from the background risk of 3-4%).

Thus, in addition to patients with lobular carcinoma and EIC, patients with pathological tumour size > 2cm, involved lymph nodes, nuclear grade 3 and oestrogen receptor negative (ER -ve) patients will receive whole breast

postoperative radiotherapy following *Targit*. With this modification we could still expect between 45-60% of patients undergoing breast conserving surgery to receive *Targit* as the only mode of radiotherapy.

Thus the modified hypothesis is that Strategy 1 is better than Strategy 2. Overall, for both the high-risk and low-risk groups together, we should get a reduction in local recurrence rates- say from 9% (overview data) to 4%. Power calculations reveal that we would need 419 patients in each arm to see that 5% reduction in local recurrence rate with a 95% confidence and 80% power.

Such a trial of course does not address a very elegant or clean scientific question (viz. is *Targit* alone equal to whole breast radiotherapy +boost), but it is pragmatic and will compare two strategies rather than treatments. If the trial is positive, strategy 1 can be adopted as standard treatment with a small risk that in good prognosis patients there may be a <1% increase in recurrence rates. If no difference is demonstrable, then it will be up to individual clinicians and patients to decide whether the cost saving and convenience is worth taking the risk of increasing the local recurrence by a maximum of 5%. The Strategy 1 will still have the potential of time, money and breasts.

The visible change in the original Targit protocol algorithm would only be the addition of high-risk groups to the Lobular and EIC box- as has been shown with an asterix*
Finally, if we extend the latest estimates from the Oxford if we reduce local recurrence by 5% we should expect to improve overall survival by 1% but of course that is not being tested in this trial.

Statistical Analysis

The major endpoint is the incidence of local recurrence. This will be compared on the basis of 'intention to treat' (i.e. all randomised patients will be analysed) and the log rank test will be used. This will be performed once the baseline data have been compared to test the randomisation and to define whether any stratified analyses are required. In addition ratios of radiological lesion size to clinical and pathological size will be compared to ensure that the extent of the surgical procedure was similar in both groups. The specimen weight will also be collected.

In addition exploratory subgroup analyses will be performed on the main endpoint including variables such as tumour size and grade and axillary nodal involvement.

Cosmetic result and patient satisfaction will be simple comparisons of the scoring achieved.

Ethical Considerations

This trial, as for most randomised studies includes an experimental treatment. However, in this case the availability of the new procedure is strictly limited. There are very few machines in clinical centres and even at those centres that have the equipment, not all patients can be given the new procedure. However, should the new technique provide adequate local control and cosmesis, and be acceptable to patients it will markedly reduce the need for external beam radiotherapy for early breast cancer. This will enable a major saving of resource. The ideal time to implement a full randomised assessment is while the technology is at fairly early stage of development. Since there are insufficient resources to give the new technique to all patients randomisation is the most ethical way to proceed. In the pilot study, every patient deemed suitable for intra-operative radiotherapy and approached gave consented for the procedure. We expect therefore a high acceptance of the novel arm. All patients will be informed

of the trial and given the opportunity to participate. Patients will be given a period (several days depending on the clinic timings) to consider entry and complete the consent form. Randomisation will only proceed once a signed consent form has been received at the clinic.

Preliminary Results

The first randomised patient was operated on 29 March 2000. We have randomised 29 patients to date (June 2001). Patient characteristics of first 24 patients are given in the table.

The patient is usually informed about possibility of the novel treatment (in context of the pilot study or the randomised trial) at the time of giving the diagnosis when the preliminary discussion about the treatment takes place in presence of the breast care nurse. This can frequently be the first visit in our one-stop clinic. For the pilot study, after the 1st case in July 1998, there were local administrative problems and proper accrual did not start until January 1999 and by January 2000, we had accrued 26 patients. During the pilot study almost all patients who were approached had agreed to participate.

In the one year period after we started the randomised trial, we have approached 32 of the 34 possibly eligible patients. The idea of being able to avoid the 6 weeks of daily treatment is very appealing to patients and most wish to take the 50% chance of receiving it. Only 3 have refused entry into the trial- the reasons in two patients was – ‘too much to take in at that time’ and one of them actually asked to be included on the morning of surgery- which of course was too short a notice.

One patient randomised to receive postoperative radiotherapy was misinformed by the breast care nurse that she was allocated to the intra-operative arm and hence came prepared for it and insisted that she be given the treatment. After long discussions it was decided to be done- as a trial violation. Unfortunately, the tumour was lobular carcinoma and she needed to take 5 weeks of postoperative radiotherapy. One patient was randomised to receive intra-operative radiotherapy did not receive it because the radiotherapy monitor did not work. This was only the second time in 2.5 years that we had a problem with equipment. The first time, was our (possible) 3rd patient in the pilot study, when one of the theatre runners knocked down the equipment and broke the quality assurance

equipment. In the randomised study, 3 patients randomised to the IORT arm had to take 5 wks of postoperative radiotherapy because of lobular histology. One elderly patient randomised to take postoperative radiotherapy has refused to take it despite prolonged discussions.

The complications, local recurrence rates and cosmetic outcome have been analysed only for the purpose of this chapter. The maximum follow up is 18 months and the median is 10 months. There was one post-operative wound infection and this was in the Post-operative arm. The maximum dose of radiation to the skin has been on an average 3Gy (95% CI 2.2-3.9). The cosmetic outcome has been excellent in both arms. No formal comparison is possible at this time, but it appears that the patients are very much satisfied (of the 11 patients assessed, the satisfaction index for appearance as well as texture was above 1 in all the 6 Targit patients but it was below 1 in 4 out of 6 post-operative radiotherapy patients). There has been no local recurrence in either arm.

Discussion

Several international investigators have now joined to form an steering committee and have submitted the first joint abstract to the ESTRO 2002 meeting. This includes results from three centres with a total of 94 patients treated using this method. With several centres collaborating it can be expected that the recruitment in the randomised trials will be excellent.

The national and international implications of development of such a novel approach can be considerable. Treatment of breast carcinoma often represents a third or more of the total case-load of radiotherapy units worldwide. Many women from the developing world and remote areas of the developed world (e.g. Outback of Australia and rural USA) cannot benefit from breast conserving therapy because of the large distances between their home and the radiotherapy centre. For more privileged woman, the avoidance of 6 weeks of daily visits to a radiotherapy centre would be a great advantage. Furthermore, in our pilot study we have found that in terms of operational expenses the novel technique needs about 3 man-hours and 45 minutes 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 were £5000, considering only the 66% saving of man-hours the novel technique would save £3750 per patient. So, if we assume that 60% of the 27000 breast cancer patients diagnosed every year in the UK, are treated by conservative surgery, the novel technique would potentially save about 60.75 million pounds ($0.60 \times 27000 \times 3750$) per year for the NHS. *In addition*, the saving of expensive resource time on linear accelerators would of course be substantial.

CHAPTER 8

Conclusion

Breast cancer treatment has undergone immense changes in the last century-these have been prompted mainly by changing models of disease. In addition, change was brought about by developments in other fields of medicine, for example, availability of good anaesthetic technique allowed Halsted to perform major surgery. More recently, patient advocacy groups have prompted change. Paradoxically this was less relevant for the development of conservative breast surgery but is becoming increasingly important in the demand for sentinel node biopsy in today's patient/consumer/client led world.

Breast cancer treatment is mainly directed towards achieving two goals- local tumour control with cosmetic outcome as an important secondary aim and systemic control with personal cure of the disease as the final goal. This thesis deals with the former- the optimal local control of disease.

The history of breast cancer treatment and the concept of local recurrence are dealt with in detail in the first chapter. It appears from various clinical trials of breast conserving surgery that clinically relevant invasive duct carcinoma is to

some extent a “focal” disease that is limited to one quadrant of the breast. This may be related to the suggestion that chromosomal abnormalities arise at an early age and are therefore distributed in a segmental fashion along the primary branches of the duct system. These chromosomal abnormalities are probably more important in developing a milieu that is conducive for transformation rather than actual transformation itself because, the segmental nature is restricted to clinically expressed invasive ductal carcinoma rather than occult or latent cancers. The spatial distribution of latent *in situ* cancer, as described in the second chapter, is on the other hand not segmental in nature, i.e., occult cancers are distributed evenly in all quadrants of the breast with no difference in such distribution between individual cancer types. It appears that for development of invasive ductal cancer, the local milieu of the surrounding breast tissue is very important and when a conducive milieu is present in any one area of the breast, it promotes the growth of tumours, both primary and recurrent. For lobular cancers and for breasts harbouring extensive intra-ductal cancer, it appears that the surrounding milieu is either less important or, is already conducive to cancer growth in all areas, so

that clinically important cancers can develop in all areas of the breast. In addition invasive lobular cancers have been characterized by their ability to secrete proteolytic enzymes allowing an alternative mechanism of local progression to the expansile growth of invasive duct cancers. Further studies in breast cancer should involve investigating the characteristics of breast milieu commonly called 'field change' that induces or promotes cancer growth in particular quadrants.

The next phase in this project was to test the hypothesis that there might be a pre-clinical test that could characterise the clinical relevance of occult cancers. We hypothesised that Magnetic resonance imaging- which relies on tumour vascularity for producing contrast enhanced images, might be able to detect tumours that are more vascular and therefore, more clinically relevant. However, contrast enhanced MRI proved to be perhaps too sensitive and was able to detect almost all occult cancers that we could subsequently detect using detailed histopathology. We concluded that we should use this new tool with caution and not allow ourselves to be precipitated into a mastectomy for the majority of patients thus overthrowing

the wisdom gleaned from the robust results of breast conservation trials.

These being the biological implications of our findings, the clinical implications were rather straightforward, albeit going against the current dogma of breast conservative surgery. The argument for whole breast radiotherapy after breast conservative therapy arose from the idea that breast cancer is a multifocal/multicentric disease, with most (90%) of the multifocality in proximity to the primary tumour. This was the explanation given for the increased incidence of local recurrence near the primary tumour. Our whole organ analysis in 3-dimensions found that occult tumours were present in all quadrants and not related to the spatial distribution of the primary tumour and are thus not relevant for early local recurrence – which occurs most commonly in the index quadrant rather than anywhere else, for reasons yet to be elucidated. If the widespread multifocality is not clinically relevant, then the standard whole breast radiotherapy after breast conserving surgery is of questionable value.

We present the problems faced by patients undergoing breast conserving therapy and health care systems

delivering it. The 6-wk course of radiotherapy is costly and inconvenient at best and prohibitive at worst. Many women living in geographically remote areas, far from a radiotherapy centre, cannot take the 6-wk holiday in the metropolis to take the radiotherapy course, and not many welfare states can provide for their accommodation or transport. Frequently these women have to choose between mastectomy and breast conservation, on the basis of, not the nature of the cancer, but on whether they can afford commute daily, or to live near the radiotherapy centre for the 30 visits during the course of radiotherapy. A solution to these problems is to deliver radiotherapy only to the quadrant of primary tumour with a technique that can do it in one sitting- preferably in the operating theatre at the time of the primary surgery. We describe one such technique of delivering therapeutic radiation in a standard operating theatre. The machine is called Photon Radiosurgery System (PRS). This technique directs soft x-rays generated with a portable lightweight electron-beam-driven device. These x-rays are generated at the centre of an applicator that can be placed in the tumour bed. So the radiation is from within the breast and as the pliable breast tissue wraps around the applicator, true conformal

radiotherapy dosimetry is achieved. The highest dose is delivered to the tissues immediately adjacent to the applicator and normal tissues like skin do not get significant radiation damage. Since the high dose region is of a small volume we expect that the late fibrosis, if any, will not be disfiguring.

We had two tasks- first to test the novel radiotherapy technique and then to test then novel approach of single dose index quadrant radiation. In the first phase, we substituted the conventional 1wk course of tumour bed boost with intra-operative radiotherapy using the PRS device; the remaining 5-wk course of whole breast radiotherapy (50Gy, #25) was delivered as usual. In the pilot phase we tested the feasibility of conducting the clinical trial- patient acceptability, the logistics of co-ordination between the radiotherapy, radiation physics and surgical departments and the clinical results. We found the usual resistance to change in the administrative circles- but the business proposition of possible saving money for NHS was attractive to the management. The patient acceptability was the least difficult area- only 2 of the patients offered the novel treatment refused to take part in

the pilot study. Many patients were keen not to take the 5wk course, suggesting to us that recruitment in the next phase of the project would be relatively easy. The pilot study and the operative technique are described in the 4th and 5th chapters. There has been no local recurrence in any of the patients on the pilot study at the median follow up of 34 months and the cosmetic outcome is good and the patients are satisfied. The results of the pilot study were instrumental in getting FDA approval for the PRS device.

We also used the PRS device in another increasingly common clinical situation. Elderly patients who are not fit for surgery, but are nevertheless known to benefit from local treatment are frequently treated with tamoxifen alone for the want of suitable local therapy. We tested the use of PRS radiotherapy as the primary treatment in these cases. We used the Fischer Mammotest prone table- for stereotactic localisation of the primary tumour and Mammotome vacuum biopsy for limited excision under local anaesthetic. After calibrating the Fischer table for the PRS device, we placed the tip of the bare PRS probe in the centre of the tumour. The radiation dose of over 130 Gy was achieved at the centre with the periphery of the

tumour receiving about 20 Gy. We found remarkable response to this treatment. The contrast-enhanced MRI, just 6 days after treatment revealed an almost absence of vascular enhancement in the tumour. All these patients with other co-morbid conditions and short life expectancy have lived the rest of their life without suffering from the morbid sequelae of breast cancer.

Encouraged by the results of the pilot phase, we started the randomised trial in March 2000, to test the hypothesis that radiotherapy to the peri-tumoural tissues alone is adequate local treatment. We called it TARGeted Intraoperative radioTherapy (TARGIT) trial. The randomisation procedure was much easier than expected. We were able to recruit more than 90% of patients eligible for the trial. Only 3-4 patients have refused to take part- mainly because the option of entry into trial is usually given early in the discussions about treatments and it was too much to take in for the patient. The early cosmetic results are good and there has not been any recurrence although the follow up time is short. Since the numbers needed to prove equivalence are 850 in each arm, a multicentre trial was deemed a necessity. A recent modification will change the

trial from an equivalence trial to a trial to test whether a strategy using Targit for all patients and additional whole breast radiotherapy for high-risk patients reduces local recurrence rates compared with conventional postoperative radiotherapy. Such a trial will need 419 patients in each arm to show a reduction in local recurrence from 9% to 4%.

This trial has attracted worldwide interest and several investigators from Australia, India, UK, Italy and USA are keen to join in. The protocol of the randomised study has been peer-reviewed and published on the Lancet Website.

The implications of proving TARGIT equal to 6-wk course of radiotherapy are far reaching. Firstly, it will save the ordeal that these women have to face to come daily for the 'radiotherapy shot'. As one woman in our trial described it to BBC's Tomorrow's world- 'I felt a bit of a fraud... have I really had cancer treatment? I had finished all my treatment and was back at work in 2 days'. In the more 'prosperous' countries, it will mean saving millions of pounds and radiotherapy resources and for the thousands of women in the developing countries and remote areas of developed world, it will mean they can preserve their breasts!

References

- Ahsan H, Neugut AI (1998) Radiation therapy for breast cancer and increased risk for esophageal carcinoma. *Ann Intern Med* 128: 114-117
- Amichetti M, Busana L, Caffo O (1995) Long-term cosmetic outcome and toxicity in patients treated with quadrantectomy and radiation therapy for early-stage breast cancer. *Oncology* 52: 177-181
- Anastassiades O, Iakovou E, Stavridou N, Gogas J, Karameris A (1993) Multicentricity of breast cancer A study of 366 cases. *Am J Clin Oncol* 99: 238-243
- Assersohn L, Powles TJ, Ashley S, Nash AG, Neal AJ, Sacks N, Chang J, Querci della RU, Naziri N (1999) Local relapse in primary breast cancer patients with unexcised positive surgical margins after lumpectomy, radiotherapy and chemoendocrine therapy [see comments]. *Ann Oncol* 10: 1451-1455
- Astor MB, Hilaris BS, Gruerio A, Varricchione T, Smith D (2000) Preclinical studies with the photon radiosurgery system (PRS). *Int J Radiat Oncol Biol Phys* 47: 809-813
- Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR (2000) Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 92: 269-271
- Atkins H, Hayward JL, Klugman DJ, Wayte AB (1972) Treatment of early breast cancer: a report after ten years of a clinical trial. *Br Med J* 2: 423-429
- Axelsson CK, Mouridsen HT, Zedeler K (1992) Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The

Danish Breast Cancer Cooperative Group (DBCG). *Eur J Cancer* 28A: 1415-1418

Axelsson CK, Rank F, Blichert-Toft M, Mouridsen HT, Jensen MB (2000) Impact of axillary dissection on staging and regional control in breast tumors < or = 10 mm--the DBCG experience. The Danish Breast Cancer Cooperative Group (DBCG), Rigshisoutalet, Copenhagen, Denmark. *Acta Oncol* 39: 283-289

Bates T, Fennessy M, Latteier J, MacRae K, Riley DL, Houghton J, Baum M. Surgery for early breast cancer improves survival in the elderly: result of a randomized trial of tamoxifen alone versus surgery plus tamoxifen. *Br.J.Surg.* 88[41], Suppl 41-41. 1-5-2001.

Bates T, Riley DL, Houghton J, Fallowfield L, Baum M (1991) Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. The Elderly Breast Cancer Working Party. *Br J Surg* 78: 591-594

Baum M, Vaidya JS, Mitra I (1997) Multicentricity and recurrence of breast cancer [letter; comment]. *Lancet* 349: 208

Beck RM, Gotz L, Heywang-Kobrunner SH (2000) Stereotaxic vacuum core breast biopsy--experience of 560 patients. *Swiss Surg* 6: 108-110

Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, Di Palma S, Simony-Lafontaine J, de M, I, van de Vijver MJ (2001) Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol* 19: 2263-2271

Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R, Veronesi U (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 294: 405-410

Boyages J, Recht A, Connolly JL, Schnitt SJ, Gelman R, Kooy H, Love S, Osteen RT, Cady B, Silver B (1990) Early breast cancer: predictors of

breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* 19: 29-41

Brenner DJ, Leu CS, Beatty JF, Shefer RE (1999) Clinical relative biological effectiveness of low-energy x-rays emitted by miniature x-ray devices. *Phys Med Biol* 44: 323-333

Buadu LD, Murakami J, Murayama S, Hashiguchi N, Sakai S, Masuda K, Toyoshima S, Kuroki S, Ohno S (1996) Breast lesions: correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis. *Radiology* 200: 639-649

Butler WE, Piaggio CM, Constantinou C, Niklason L, Gonzalez RG, Cosgrove GR, Zervas NT (1998) A mobile computed tomographic scanner with intraoperative and intensive care unit applications. *Neurosurgery* 42: 1304-1310

Chan KC, Knox WF, Sinha G, Gandhi A, Barr L, Baildam AD, Bundred NJ (2001) Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. *Cancer* 91: 9-16

Clark RM, McCulloch PB, Levine MN, Lipa M, Wilkinson RH, Mahoney LJ, Basrur VR, Nair BD, McDermot RS, Wong CS (1992) Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 84: 683-689

Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, Lipa M, Wilkinson RH, Mahoney LJ (1996) Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 88: 1659-1664

Clark RM, Wilkinson RH, Mahoney LJ, Reid JG, MacDonald WD (1982) Breast cancer: a 21 year experience with conservative surgery and radiation. *Int J Radiat Oncol Biol Phys* 8: 967-979

Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, May-Levin F, Contesso G, Arriagada R (1985) Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. *Int J Radiat Oncol Biol Phys* 11: 137-145

Cosgrove GR, Hochberg FH, Zervas NT, Pardo FS, Valenzuela RF, Chapman P (1997) Interstitial irradiation of brain tumors, using a miniature radiosurgery device: initial experience. *Neurosurgery* 40: 518-523

Cosgrove R, Spiro I, I, Loeffler J, Biggs P, Beatty J, Zervas NT (1999) Stereotactic interstitial radiosurgery for malignant brain tumors. *Stereotact Funct Neurosurg* 73: 37

Craft PS, Primrose JG, Lindner JA, McManus PR (1997) Surgical management of breast cancer in Australian women in 1993: analysis of Medicare statistics. *Med J Aust* 166: 626-629

Cuzick J, Stewart H, Peto R, Baum M, Fisher B, Host H, Lythgoe JP, Ribeiro G, Scheurlen H, Wallgren A (1987) Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 71: 15-29

Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H (1994) Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy [see comments]. *J Clin Oncol* 12: 447-453

Dale RG, Jones B, Price P (1997) Comments on Inadequacy of Iridium Implant as sole radiation treatment for operable breast cancer, Fentiman et al., *Eur J Cancer* 1996, 32A, pp 608-611. *Eur J Cancer* 33: 1707-1708

Deng G, Lu Y, Zlotnikov G, Thor AD, Smith HS (1996) Loss of heterozygosity in normal tissue adjacent to breast carcinomas. *Science* 274: 2057-2059

Douglas RM, Beatty J, Gall K, Valenzuela RF, Biggs P, Okunieff P, Pardo FS (1996) Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases. *Int J Radiat Oncol Biol Phys* 36: 443-450

Early Breast Cancer Trialists' Collaborative Group (1988) Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group [see comments]. *N Engl J Med* 319: 1681-1692

Early Breast Cancer Trialists' Collaborative Group (1995) Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 333: 1444-1455

Early Breast Cancer Trialists' Collaborative Group (2000) Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. [see comments]. *Lancet* 355: 1757-1770

Egan RL (1982) Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. *Cancer* 49: 1123-1130

Egan RL, Ellis JT, Powell RW (1969) Team approach to the study of diseases of the breast. *Cancer* 23: 847-854

Ewing J (1928) *Neoplastic Diseases*. W B Saunders: Philadelphia

Fentiman, I. S. Long-term follow-up of the first breast conservation trial (Guy's Wide Excision Study). *Eur J Cancer* 34[Suppl 5], S37-S38. 1998.

Fentiman IS (2000) Long-term follow-up of the first breast conservation trial: Guy's wide excision study. *Breast* 9: 5-8

Fentiman IS, Matthews PN, Davison OW, Millis RR, Hayward JL (1985) Survival following local skin recurrence after mastectomy. *Br J Surg* 72: 14-16

Fentiman IS, Poole C, Tong D, Winter PJ, Mayles HM, Turner P, Chaudary MA, Rubens RD (1991) Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Eur J Cancer* 27: 447-450

Fentiman IS, Poole C, Tong D, Winter PJ, Gregory WM, Mayles HM, Turner P, Chaudary MA, Rubens RD (1996) Inadequacy of iridium implant as sole radiation treatment for operable breast cancer [see comments]. *Eur J Cancer* 32A: 608-611

Fisher B (1980) Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res* 40: 3863-3874

Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, Mamounas EP, Deutsch M, Margolese R (1991a) Significance of ipsilateral breast tumour recurrence after lumpectomy [see comments]. *Lancet* 338: 327-331

Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM (1995) 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 [see comments]. *N Engl J Med* 333: 1456-1461

Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, Fisher E, Wolmark N, Deutsch M, Montague E (1985) Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 312: 665-673

Fisher B, Gunduz N, Costantino J, Fisher ER, Redmond C, Mamounas EP, Siderits R (1991b) DNA flow cytometric analysis of primary operable breast cancer. Relation of ploidy and S-phase fraction to outcome of patients in NSABP B-04. *Cancer* 68: 1465-1475

Fisher B, Wolmark N, Redmond C, Deutsch M, Fisher ER (1981) Findings from NSABP Protocol No. B-04: comparison of radical

mastectomy with alternative treatments. II. The clinical and biologic significance of medial-central breast cancers. *Cancer* 48: 1863-1872

Fisher B, Gebhardt MC (1978) The evolution of breast cancer surgery: past, present, and future. *Semin Oncol* 5: 385-394

Fisher ER, Anderson S, Redmond C, Fisher B (1992) Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Semin Surg Oncol* 8: 161-166

Fisher ER, Costantino J, Fisher B, Palekar AS, Paik SM, Suarez CM, Wolmark N (1996) Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Five-year observations concerning lobular carcinoma in situ. *Cancer* 78: 1403-1416

Fisher ER, Sass R, Fisher B, Wickerham L, Paik SM (1986) Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). I. Intraductal carcinoma (DCIS). *Cancer* 57: 197-208

Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, Smith DC, George WD (1996) Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group [see comments]. *Lancet* 348: 708-713

Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL (1990) Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment [see comments]. *Int J Radiat Oncol Biol Phys* 19: 833-842

Gallager HS, Martin JE (1969) Early phases in the development of breast cancer. *Cancer* 24: 1170-1178

Gazet JC, Ford HT, Coombes RC, Bland JM, Sutcliffe R, Quilliam J, Lowndes S (1994) Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *Eur J Surg Oncol* 20: 207-214

Gross SW (1880) *Practical Treatise on Tumours of the Mammary Gland*. Appleton & Co.: New York

Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, Glazer PM, Ward B, Carter D, Matloff E, Bale AE, Alvarez-Franco M (2002) Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet* 359: 1471-1477

Halsted WS (1894a) The results of operations for the cure of cancer of the breast performed at The Johns Hopkins Hospital from June 1889 to January 1894. *Johns Hopkins Hospital Reports* 4: 297-350

Halsted, W. S. (1894b) The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Ann.Surg.* 20, 497-555.

Harris JR, Botnick L, Bloomer WD, Chaffey JT, Hellman S (1981) Primary radiation therapy for early breast cancer: the experience at The Joint Center for Radiation Therapy. *Int J Radiat Oncol Biol Phys* 7: 1549-1552

Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from effective axillary treatment. *Breast Cancer Res Treat* 5: 17-21

Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M (1989) Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *BMJ* 298: 1611-1614

Heywang-Kobrunner SH, Viehweg P, Heinig A, Kuchler C (1997) Contrast-enhanced MRI of the breast: accuracy, value, controversies, solutions. *Eur J Radiol* 24: 94-108

Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans Stekhoven JH (1990) Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. *Lancet* 335: 519-522

Holland R, Veling SH, Mravunac M, Hendriks JH (1985) Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 56: 979-990

Houghton J, Baum M, Haybittle JL (1994) Role of radiotherapy following total mastectomy in patients with early breast cancer. The Closed Trials Working Party of the CRC Breast Cancer Trials Group. *World J Surg* 18: 117-122

Hunter MA, McFall TA, Hehr KA (1996) Breast-conserving surgery for primary breast cancer: necessity for surgical clips to define the tumor bed for radiation planning. *Radiology* 200: 281-282

Hutter RVP, Dim DU (1971) The problem of multiple lesions of the breast. *Cancer* 28: 1591-1607

Johansson, B., Karlsson, L., and Liljegren, G. PDR brachytherapy as the sole adjuvant radiotherapy after breast conserving surgery for T1-2 breast cancer. Program and abstracts -10th International Brachytherapy Conference, Madrid, Nucletron, 127. 2000.

Keynes GL (1937) Conservative treatment of cancer of the breast. *BMJ* 2: 643-647

Keynes GL (1952) Carcinoma of breast. *St Bart Hosp Rep* 56: 462-466

King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ (2000) 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* 180: 299-304

Koniaris LG, Chan DY, Magee C, Solomon SB, Anderson JH, Smith DO, De Weese T, Kavoussi LR, Choti MA (2000) Focal hepatic ablation using interstitial photon radiation energy. *J Am Coll Surg* 191: 164-174

Krawczyk JJ, Engel B (1999) The importance of surgical clips for adequate tangential beam planning in breast conserving surgery and irradiation. *Int J Radiat Oncol Biol Phys* 43: 347-350

Krishnan L, Jewell WR, Tawfik OW, Krishnan EC (2001) Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. *Breast J* 7: 91-96

Kurita H, Ostertag CB, Baumer B, Kopitzki K, Warnke PC (2000) Early effects of PRS-irradiation for 9L gliosarcoma: characterization of interphase cell death. *Minim Invasive Neurosurg* 43: 197-200

Kurtz JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, Pietra JC, Hans D, Pollet JF, Bressac C, Spitalier JM (1989a) Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 63: 1912-1917

Kurtz JM, Jacquemier J, Torhorst J, Spitalier JM, Amalric R, Hunig R, Walther E, Harder F, Almendral A, Brandone H (1989b) Conservation therapy for breast cancers other than infiltrating ductal carcinoma. *Cancer* 63: 1630-1635

Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C (1983) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer* 51: 1941-1943

Lacour J, Le M, Rumeau C, Bucalossi P, Caceres E, Koszarowski T, Jacobelli G, Veronesi U (1976) [International therapeutic trial comparing the value of radical mastectomy (Halsted) and extended mastectomy (Halsted plus internal mammary node dissection in the treatment of breast cancer. 5-year results]. *Chirurgie* 102: 638-649

Lagios MD (1977) Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. *Cancer* 40: 1726-1734

Latteier J, Bates T, Riley DL, Houghton J, Baum M, Closed Trials Working Party of the CRC Breast Cancer Trials Group L (1997) The addition of surgery to tamoxifen as primary treatment of early breast cancer in women over 70, a multicentre trial. *Breast* 6: 224

Lewis D, Rienhoff WFJr (1932) A study of results of operations for the cure of cancer of the breast. *Ann Surg* 95: 336

Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, Adami HO (1999) 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial [see comments]. *J Clin Oncol* 17: 2326-2333

Lu Q, Nakmura J, Savinov A, Yue W, Weisz J, Dabbs DJ, Wolz G, Brodie A (1996) 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* 137: 3061-3068

Machtay M, Lanciano R, Hoffman J, Hanks GE (1994) Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 30: 43-48

Mai KT, Yazdi HM, Isotalo PA (2000) Resection margin status in lumpectomy specimens of infiltrating lobular carcinoma. *Breast Cancer Research and Treatment* 60: 29-33

McDermott MW, Cosgrove GR, Larson DA, Sneed PK, Gutin PH (1996) Interstitial brachytherapy for intracranial metastases. *Neurosurg Clin N Am* 7: 485-495

Meier P, Ferguson DJ, Karrison T (1985) A controlled trial of extended radical mastectomy. *Cancer* 55: 880-891

Meier P, Ferguson DJ, Karrison T (1989) A controlled trial of extended radical versus radical mastectomy. Ten- year results. *Cancer* 63: 188-195

Moore C (1867) On the influence of inadequate operations on the theory of cancer. *R Med Chir Soc Lond* 1: 244-280

Moore MM, Borossa G, Imbrie JZ, Fechner RE, Harvey JA, Slingluff CL, Adams RB, Hanks JB (2000) Association of infiltrating lobular carcinoma with positive surgical margins after breast-conservation therapy. *Annals of Surgery* 231: 877-881

Morrow M, White J, Moughan J, Owen J, Pajack T, Sylvester J, Frank Wilson J, Winchester D (2001) Factors Predicting the Use of Breast-Conserving Therapy in Stage I and II Breast Carcinoma. *J Clin Oncol* 19: 2254-2262

Nakamura J, Savinov A, Lu Q, Brodie A (1996) Estrogen regulates vascular endothelial growth/permeability factor expression in 7,12-dimethylbenz(a)anthracene-induced rat mammary tumors. *Endocrinology* 137: 5589-5596

Nattinger AB, Kneusel RT, Hoffmann RG, Gilligan MA (2001) Relationship of distance from a radiotherapy facility and initial breast cancer treatment. *J Natl Cancer Inst* 93: 1344-1346

Neugut AI, Murray T, Santos J, Amols H, Hayes MK, Flannery JT, Robinson E (1994) Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers [see comments]. *Cancer* 73: 1615-1620

Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA (1987) Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *Br J Cancer* 56: 814-819

O'Neill JS, Elton RA, Miller WR (1988) Aromatase activity in adipose tissue from breast quadrants: a link with tumour site. *Br Med J (Clin Res Ed)* 296: 741-743

Obedian E, Haffty BG (2000) Negative margin status improves local control in conservatively managed breast cancer patients. *Cancer J Sci Am* 6: 28-33

Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial [see comments]. *N Engl J Med* 337: 949-955

Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial [see comments]. *Lancet* 353: 1641-1648

Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, Gelman R, Silver B, Hetelekidis S, Abner A, Harris JR, Schnitt SJ (2000) Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol* 18: 1668-1675

Perera F, Engel J, Holliday R, Scott L, Girotti M, Girvan D, Chisela F, Venkatesan V (1997) Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: a pilot study. *J Surg Oncol* 65: 263-267

Polgar, C., Major, T., and Mangel, L. C. Sole HDR brachytherapy after breast conserving surgery:4-year results of a pilot study and initial findings of a randomised phase III trial. *Radiother.Oncol.* 55 (suppl 1), 31. 2000.

Porter R (1998) In *The Greatest Benefit to mankind*, pp 73-82. Harper Collins:

Potyka I, Houghton J, Baum M, Odling W, CRC Breast Cancer Trials Group (1999) The role of postoperative radiotherapy after breast conserving surgery in the presence of systemic therapy. *Br J Cancer* 80: Suppl 2:11

Qualheim RE, Gall EA (1957) Breast carcinoma with multiple sites of origin. *Cancer* **10**: 460-468

Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer [see comments]. *N Engl J Med* 337: 956-962

Rauschecker HF, Sauerbrei W, Gatzemeier W, Sauer R, Schauer A, Schmoor C, Schumacher M (1998) Eight-year results of a prospective non-randomised study on therapy of small breast cancer. The German Breast Cancer Study Group (GBSG). *Eur J Cancer* 34: 315-323

Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS (1993) The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol (R Coll Radiol)* 5: 278-283

Robertson JF, Ellis IO, Elston CW, Blamey RW (1992) Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5-year follow-up. *Eur J Cancer* 28A: 908-910

Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF (1975) "Residual" mammary carcinoma following simulated partial mastectomy. *Cancer* 35: 739-747

Samuel LM, Dewar JA, Preece PE, Wood RAB (1999) A pilot study of radical radiotherapy using a perioperative implant following wide local excision for carcinoma of the breast. *Breast* 8: 95-97

Sarnelli R, Squartini F (1986) Multicentricity in breast cancer: a submacroscopic study. *Pathol Annu* 21 Pt 1: 143-158

Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB (1984) Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer* 53: 1049-1057

Sedlmayer F, Rahim HB, Kogelnik HD, Menzel C, Merz F, Deutschmann H, Kranzinger M (1996) Quality assurance in breast cancer brachytherapy: geographic miss in the interstitial boost treatment of the tumor bed. *Int J Radiat Oncol Biol Phys* 34: 1133-1139

Shah JP, Rosen PP, Robbins GF (1973) Pitfalls of local excision in the treatment of carcinoma of the breast.. *Surg Gynecol Obstet* 136: 721-725

Shukla HS, Melhuish J, Mansel RE, Hughes LE (1999) Does local therapy affect survival rates in breast cancer? [see comments]. *Ann Surg Oncol* 6: 455-460

Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, Gamagami P, Colburn WJ (1999) The influence of margin width on local control of ductal carcinoma in situ of the breast [see comments]. *N Engl J Med* 340: 1455-1461

Solomon SB, Koniaris LG, Chan DY, Magee CA, DeWeese TL, Kavoussi LR, Choti MA (2001) Temporal CT changes after hepatic and renal interstitial radiotherapy in a canine model. *J Comput Assist Tomogr* 25: 74-80

Spinelli C, Berti P, Ricci E, Miccoli P (1992) Multicentric breast tumour: an anatomical-clinical study of 100 cases. *Eur J Surg Oncol* 18: 23-26

Turner BC, Glazer PM, Haffty BG (1999a) BRCA1/BRCA2 in breast-conserving therapy [letter; comment]. *J Clin Oncol* 17: 3689

Turner BC, Harrold E, Matloff E, Smith T, Gumbs AA, Beinfeld M, Ward B, Skolnick M, Glazer PM, Thomas A, Haffty BG (1999b) 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 [see comments]. *J Clin Oncol* 17: 3017-3024

Urban J (1978) Management of operable breast cancer: the surgeon's view. *Cancer* 42: 2066

Vaidya JS, Baum M (1998) Clinical and biological implications of the milan breast conservation trials. *Eur J Cancer* 34: 1143-1144

Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP, Thomson E (2001) Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 12: 1075-1080

Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mitra I (1996) Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 74: 820-824

van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, van der SE, Sylvester R, Winter J, van Zijl K (1992) Randomized

clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr* 15: 18

van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, Sylvester R, Fentiman IS, van der Schueren E, van Zijl K, Blichert-Toft M, Bartelink H, van Dongen JA (1999) Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 35: 32-38

Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, Rilke F, Sacchini V, Saccozzi R, Savio T (1993) Radiotherapy after breast-preserving surgery in women with localized cancer of the breast [see comments]. *N Engl J Med* 328: 1587-1591

Veronesi U, Orecchia R, Luini A, Gatti G, Intra M, Zurrada S, Ivaldi G, Tosi G, Ciocca M, Tosoni A, De Lucia F (2001) A preliminary report of intraoperative radiotherapy (IORT) in limited- stage breast cancers that are conservatively treated. *Eur J Cancer* 37: 2178-2183

Vicini FA, Baglan KL, Kestin LL, Mitchell C, Chen PY, Frazier RC, Edmundson G, Goldstein NS, Benitez P, Huang RR, Martinez A (2001) Accelerated treatment of breast cancer. *J Clin Oncol* 19: 1993-2001

Wazer DE, Lowther D, Boyle T, Ulin K, Neuschatz A, Ruthazer R, DiPetrillo TA (2001) Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 50: 107-111

Weidner N, Semple JP, Welch WR, Folkman J (1991) Tumor angiogenesis and metastasis--correlation in invasive breast carcinoma. *N Engl J Med* 324: 1-8

Westman-Naeser S, Bengtsson E, Eriksson O, Jarkrans T, Nordin B, Stenkvist B (1981) Multifocal breast carcinoma. *Am J Surg* 142: 255-257

Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML (2000) Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 18: 1220-1229

Willner J, Kiricuta IC, Kolbl O (1997) Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 37: 853-863

Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA* 285: 885-892

Acknowledgments

I cannot acknowledge in words, the tremendous encouragement, support, unlimited patience, and the wisdom of guidance by Professor Michael Baum that I continue to receive. The various projects would not have been successful without the very willing help, guidance and support from Dr Jeffery Tobias, Dr Indraneel Mittra, Mrs Joan Houghton, Prof Irving Taylor, Dr Margaret Hall Craggs, Mr Mo Keshtgar, Mr Richard Sainsbury, Mr Paul Boulos, Ms Lisa Gale, Mr Michael Douek, Mr Derek D'Souza, Mr Steven Morgan, Mr Marinos Metaxas, Mr Sini Naidu and Dr Ivan Rosenberg, Dr Euan Thomson, Mr Tom Varricchionne, Dr Ken Harte, Mr Alan Sliski, Dr Vaman Lokare, Dr Michael O'Hare, Dr John Hartley, Joan Hartley and Dr. Victoria Spanswick, Ms Ciara McNulty, Ms Jane Stumcke, Ms Emma Collins and of course all the patients who participated in the studies. I wish to thank Photoelectron Corporation for the research grant and continuing generous support. I am grateful for the institutional support of the University College London, the Middlesex Hospital and the University College Hospitals NHS trust. I wish to acknowledge all those whose names I might have inadvertently omitted.

I cannot thank enough my wife Sucheta for her love, encouragement, patient tolerance of my long hours and support, both emotional and intellectual, and my children, Hrisheekesh and Uma for their boundless love.

Appendix

Pilot study - Patient Characteristics

Sr No	Date of Surgery	HospNo	Age (yrs)	height (cm)	weight (kg)	bra-size	bra-cup	Ethnic origin	Menopausal status	Other Medical history
1	02/07/1998	93074699	59	165.0	59.0	38	C	Caucasian	Post-	
2	17/09/1998	98052875	71	155.0	64.0	36	C	Caucasian	Post-	
3	10/02/1999	99002414	51	160.0	67.0	38	C	Caucasian	Peri-	Asthma
4	03/03/1999	U/FN1171	43	160.0	59.1	34	A	Caucasian	Peri-	
5	24/03/1999	99009704	36	157.0	48.0	34	A	Caucasian	Pre-	
6	07/04/1999	96003407	34	173.0	65.0	36	A	Caucasian	Pre-	Polycystic kidney
7	07/04/1999	E/VA0143	47	163.0	56.0	34	A	Caucasian	Post-	
8	14/04/1999	91033939	65	155.0	70.0	40	B	Caucasian	Post-	Asthma, High BP
9	14/04/1999	99014609	41	160.0	95.0	38	D	Caucasian	Pre-	
10	05/05/1999	92041175	80	152.0	48.0	32	A	Caucasian	Post-	Blind
11	12/05/1999	99025004	47	168.0	67.0	36	B	Jewish	Pre-	Ovarian cysts
12	23/06/1999	99029406	46	170.0	61.0	34	B	Black Carribean	Pre-	
13	30/06/1999	U/FC8805	72	177.8	73.2	38	D	Caucasian	Post-	Rt Breast cancer - BCT 1984
14	30/06/1999	91118496	56	169.0	64.0	34	E	Caucasian	Post-	
15	07/07/1999	99024760	47	163.0	70.0	38	B	Caucasian	Post-	Borderline mucinous ca ovary
16	14/07/1999	99026480	49	163.0	61.0	34	C	Indian	Peri-	
17	20/10/1999	95040397	43	158.8	48.00	34	A	Indian	Peri-	
18	03/11/1999	99055515	31	158.0	45.0	34	B	Chinese	Pre-	
19	03/11/1999	99059814, MZC00882	45	147.3	126.0	36	B	Jewish	Pre-	depression
20	10/11/1999	95015227	53	167.6	126.0	34	A	Black Carribean	Peri-	
21	17/11/1999	98023506	55	168.9	70.0	38	DD	Caucasian	Post-	On HRT
22	17/11/1999	U/BZ6707	69	167.0	105.7	42	D	Caucasian	Post-	
23	01/12/1999	U/FP7647	53	161.3	54.0	36	B	Caucasian	Pre-	
24	19/01/2000	99028455	52	156.0	55.0	34	C	French	Peri-	
25	26/01/2000	93068967	34	172.0	60.0	30	FF	Indian	Pre-	
26	22/03/2000	93074379	73					Jewish	Post-	R breast 1987

	Age	Ht. (cm)	Wt. (Kg)	Bra Size
Mean	52.0	162.7	68.7	35.7
SD	13	7.2	21.9	2.63
95% CI	5.1	2.8	8.4	1.01
UCL	46.9	160.0	60.3	34.7
LCL	57.1	165.5	77.1	36.7
Median	50.0	163.0	64.0	36.0
Min	31.0	147.3	45.0	30.0
Max	80.0	177.8	126.0	42.0

Bra Cup	
A	7
B	7
C	5
D	3
DD	1
E	1
FF	1
?	1

Pilot study-Intra-operative radiotherapy details

Sr No	Applicator (cm)	Heart shield	IORT Dose @ 1cm	IORT time (min)	Cumulative photon count	Average Photon Count	Max TLD	Avge TLD skin dose
1	3.5	Yes	5.0	36.8	60302977	1638668		
2	4	Yes	5.0	28.18	82787142	2937798		
3	3.5		5.0	22.7	81598491	3594647		
4	3.5	Yes	5.0	21.1	71591442	3392959		
5	3.5	Yes	5.0	23.11	83685594	3621185		
6	3.5		5.0	21.14	76852826	3635422		
7	3	Yes	5.0	26.48	95588259	3609829		
8	3.5		5.0	22.59	76942624	3406048		
9	4		5.0	28.74	96644147	3362705		
10	3.5	Yes	7.5	32.63	115611422	3543102		
11	3.5		5.0	21.58	72269326	3348903		
12	2.5		5.0	23.42	84323289	3600482		
13	4.5	Yes	6.0	42.57	152542300	3583329	6.5	5
14	3		4.0	22.4	80287366	3584257	2.3	1.6
15	3.5	Yes	5.0	21.09	71087060	3370652	4.8	3.1
16	4	Yes	5.0	26.97	96249937	3568778	3.4	2.9
17	4		5.0	26.24	88757587	3382530	3.5	3.3
18	3.5	Yes	5.0	21.65	73390350	3389855	9.2	6.5
19	3		5.0	27.16	91285790	3361038	4.5	4.2
20	3.5		5.0	21.95	70136311	3195276	7.6	6.1
21	3.5	Yes	5.0	21.03	71562702	3402886	1.4	1.2
22	4.5	Yes	5.0	33.37	112981391	3385717	8.9	7.9
23	3.5	Yes	5.0	21.03	70932894	3372938		
24	4.5		5.0	33.91	119442153	3522328	3.7	3.1
25	4.5		5.0	34.34	115911180	3375398	2.1	1.7
26	4		5.0	27.08	91395830	3375031	1.8	1.5
				IORT time (min)	Cumulative photon count	Average Photon Count	Max TLD (Gy)	Avge TLD (Gy)
			Mean	26.5	88621553	3367760	4.6	3.7
			SD	5.9	20594388	384593	2.7	2.1
			95% CI	2.3	7916071	147830	1.0	0.8
			UCL	24.3	80705483	3219930	3.6	2.9
			LCL	28.8	96537624	3515590	5.6	4.5
			Median	24.8	83236368	3391407	3.7	3.1
			Min	21.0	60302977	1638668	1.4	1.2
			Max	42.6	152542300	3635422	9.2	7.9
Applicator Sizes								
2.5cm	1							
3cm	3							
3.5cm	13							
4cm	5							
4.5cm	4							

Pilot study - Histopathology

Sr No	Specimen Wt. (gm)	Sp. X (cm)	Sp. Y (cm)	T X (cm)	T Y (cm)	Lymph Node dissected	Lymph nodes involved	Histology	Grade	DCIS	LCIS
1		5	4	1	1	9	0	IDC	2	0	0
2	32	6	4	4	5	12	0	IDC	1	1	0
3	26	6	5	1	1	9	0	IDC	3	1	0
4	56	6	6	2	2	8	0	IDC	1	1	0
5	25	5	4	1	1	9	0	IDC	3	1	0
6	42	6	5	1	1	18	0	IDC	3	0	0
7	17	4	4	0.4	0.4	13	0	Tubular	1	1	0
8	72	4	4	3	3	6	0	ILC	1	1	0
9	102	8	8	2	2	25	0	IDC	3	0	0
10	68	10	6	3	2	10	0	IDC	2	1	0
11		21	6	4	4	15	1	IDC	3	EIC	0
12	21	5	4	2	0	1	0	IDC	1	1	1
13	0	10	9	3	0	13	0	IDC	3	1	0
14	42	7	4	2	2	10	0	ILC	1	0	1
15	72	7	7	2	0	12	0	IDC	2	1	0
16	90	9	8	1	0	1	0	IDC	2	1	1
17	75	9	9	3	0	13	0	IDC	3	0	0
18	23	6	6	2	0	10	0	IDC	3	1	0
19	19	5	5	3	0	20	0	IDC	3	0	0
20	35	6	6	2	2	6	0	IDC	3	1	0
21	80	7	6	2	2	1	0	IDC	2	0	0
22	220	13	11	4	4	18	0	IDC	2	0	0
23	29	7	6	2	1	13	2	IDC	2	0	0
24	93	8	7	3	3	9	0	ILC	2	0	1
25	34	7	5	3	3	6	1	IDC	3	1	0
26	79	9	6	3	2	14	0	IDC + ILC	3	1	0

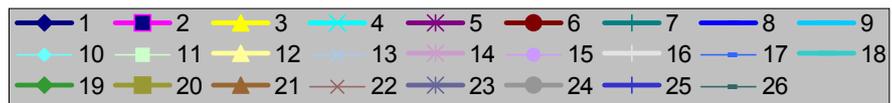
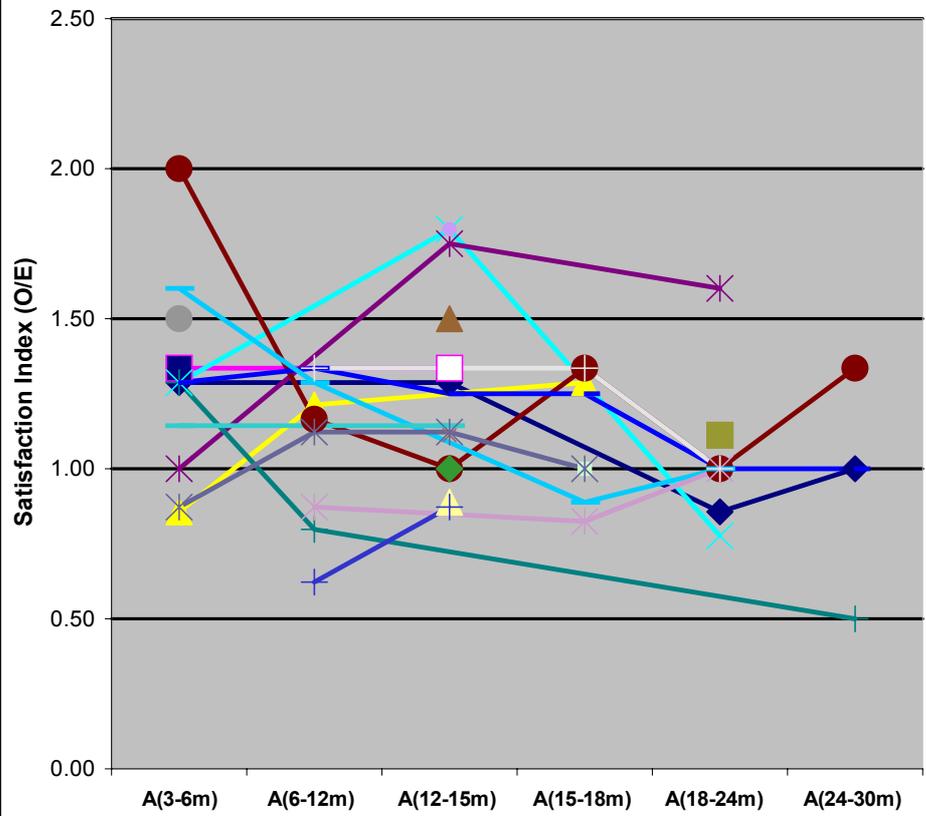
Sr No	Specimen Wt. (gm)	Sp. X (cm)	Sp. Y (cm)	T X (cm)	T Y (cm)	Lymph Node dissected	Lymph nodes involved				
Mean	56.3	7.6	5.9	2.2	1.5	12.1	0.2		IDC		21
SD	45.0	3.5	1.8	0.9	1.3	4.7	0.5		Tubular		1
95% CI	17.3	1.3	0.7	0.3	0.5	1.9	0.2		ILC		3
UCL	39.1	6.2	5.2	1.9	1.0	10.2	0.0		ILC+IDC		1
LCL	73.6	8.9	6.6	2.5	2.0	14.0	0.4				
Median	42.0	6.8	5.5	2.0	1.5	12.0	0.0		Grade 1		6
Min	0.0	4.0	3.5	0.4	0.0	6.0	0.0		Grade 2		12
Max	220.0	21.0	11.0	4.0	4.5	25.0	2.0		Grade 3		8

Pilot study -Patient Satisfaction

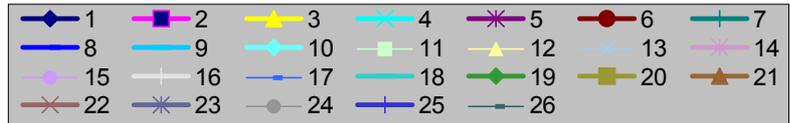
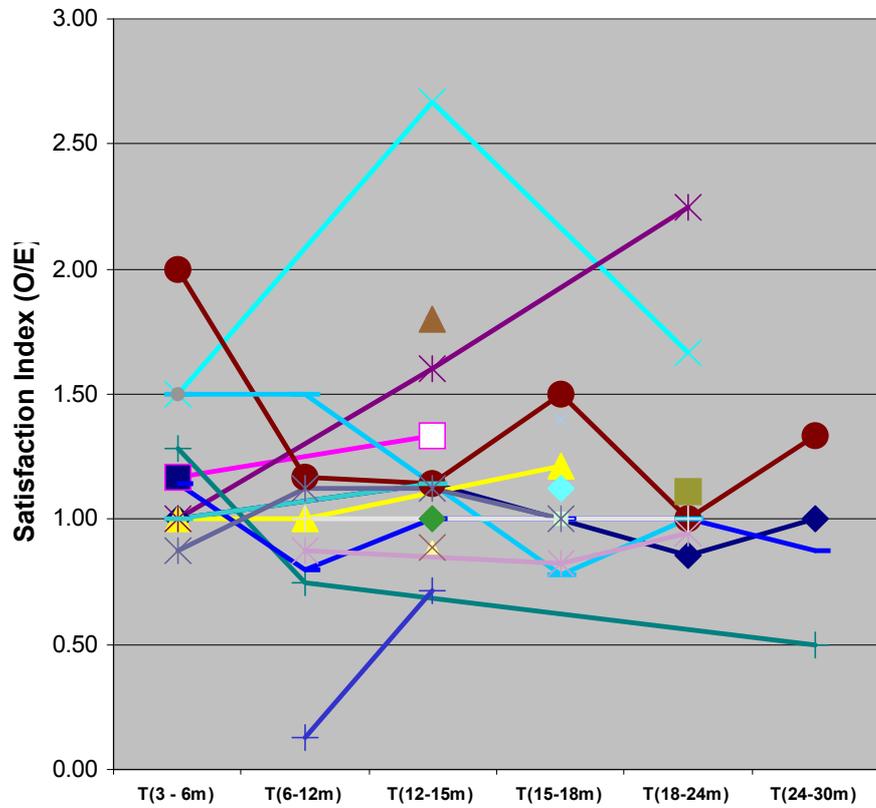
Case No.	Appearance Expected	Appearance Actual	Appearance- O/E	Texture Expected	Texture Actual	Texture Exo/Obs
1	7	9.00	1.29	7	8.00	1.14
2	6	8	1.33	6	8	1.33
3	7	9	1.29	7	8.5	1.21
4	5	9.00	1.80	3	8.00	2.67
5	4	7.00	1.75	5	8.00	1.60
6	8	8	1.00	7	8	1.14
7	8	4.00	0.50	8	4.00	0.50
8	8	10.00	1.25	9	9.00	1.00
9	8	8	1.00	9	9	1.00
10				8	9	1.13
11		10			10	
12	9	8.00	0.89	9	8.00	0.89
13	5	5	1.00	5	7	1.40
14	8.5	7.00	0.82	8.5	7.00	0.82
15	5	9	1.80	5	9	1.80
16	6	8	1.33	8	8	1.00
17	4	8	2.00	5	7	1.40
18	7	8	1.14	7	8	1.14
19	8	8	1.00	7	7	1.00
20	9	10	1.11	9	10	1.11
21	6	9	1.50	5	9	1.80
22	9	10.00	1.11	9	8.00	0.89
23	8	9	1.13	8	9	1.13
24	6	9.00	1.50	6	9.00	1.50
25	8	7.00	0.88	7	5.00	0.71
26						
Sample size	23	24	23	24	25	24
Means	6.9	8.2	1.2	7.0	8.0	1.2
Std Dev	1.58	1.47	0.36	1.67	1.36	0.44
95% CI	0.65	0.59	0.15	0.67	0.53	0.18
Lower CL	6.3	7.6	1.1	6.3	7.5	1.0
Upper CL	7.6	8.8	1.4	7.6	8.6	1.4

*Patients were asked to give a score between 1 to 10, 10 being the best
Assessment in this table are at 12 - 24 months

Satisfaction Index - Appearance



Satisfaction Index - Texture



Target Trial Allocation				
Trial No.	Hosp No.	Allocated	Received	Date of Surgery
BCTA 001001	99003147	Postop	Postop	29/03/00
BCTA 001002	97037297	Postop	Postop	05/04/00
BCTA 001003	97041624	IORT	IORT	22/05/00
BCTA 001004	M/184521	IORT	IORT	26/06/00
BCTA 001005	U/EH9157	Postop	Postop	19/07/00
BCTA 001006	92013347	IORT	IORT	31/07/00
BCTA 001007	E/G1544	Postop	Postop	02/08/00
BCTA 001008	92009449	Postop	IORT+Postop	07/08/00
BCTA 001009	00038414	IORT	IORT	09/08/00
BCTA 001010	00039748	Postop	Postop	16/08/00
BCTA 001011	93080167	IORT	IORT	30/08/00
BCTA 001012	91144767	IORT	IORT	15/11/00
BCTA 001013	91116415	IORT	IORT	22/11/00
BCTA 001014	U/AS3533	Postop	Postop	29/11/00
BCTA 001015	97066902	IORT	IORT	29/11/00
BCTA 001016	00054580	Postop	Nil	01/12/01
BCTA 001017	M/364301	Postop	Postop	01/12/01
BCTA 001018	95029497	IORT	IORT+Postop	26/01/01
BCTA 001019	00066220	IORT	Postop	01/02/01
BCTA 001020	U/AE5416	Postop	Postop	19/03/01
BCTA 001021	UBD5206	Postop	Postop	04/04/01
BCTA 001022	M308851	Postop	Postop	28/03/01
BCTA 001023	96003378	IORT	IORT	04/04/01
BCTA 001024	93089517	IORT	IORT+Postop	28/03/01

Target trial - Patient Characteristics					
Trial No.	DOB	Religion	Ethnic origin	Age	Meno-pausal status
BCTA 001001	06/10/48	none	White	52	Post
BCTA 001002	07/06/49	COE	White	51	Post
BCTA 001003	30/06/69	Evangeli	White	31	Pre
BCTA 001004	07/10/56	none	White	44	Pre
BCTA 001005	14/07/29	COE	White	71	Post
BCTA 001006	01/05/55	COE	White	45	Pre
BCTA 001007	07/09/55	none		45	Pre
BCTA 001008	07/03/49	other	White	51	Pre
BCTA 001009	18/06/30	COE	White	70	Post
BCTA 001010	29/07/55		White	45	Pre
BCTA 001011	09/11/22	RC	White	78	Post
BCTA 001012	19/03/49	RC	White	52	Post
BCTA 001013	02/09/32	RC	White	68	Post
BCTA 001014	24/12/27	COE	White	73	Post
BCTA 001015	15/12/51	COE	Black	49	Pre
BCTA 001016	17/07/23		White	78	Post
BCTA 001017	15/12/28	COE	White	73	Post
BCTA 001018	01/11/43	Greek	White	57	Pre
BCTA 001019	01/09/56	Hindu	Asian	44	Pre
BCTA 001020	03/07/36	RC	White	65	Post
BCTA 001021	11/02/41	COe	White	60	Post
BCTA 001022	09/07/32	COE	White	69	Post
BCTA 001023	01/01/58	RC	White	43	Pre
BCTA 001024	17/07/35	Protesta	White	66	Post

Target trial - Histopathology													
Trial No.	side	sp weight	Margins	T	Histology	Gr	DC IS	LC IS	EIC	ER	PR	LN diss	LN inv
BCTA 001001	L	85		1.5	IDC	3	1					9	
BCTA 001002	R	67		2.1	IDC	2	1			1	1	11	
BCTA 001003	L			2.5	IDC	3	1					16	
BCTA 001004	L			3.0	IDC	3	1					8	
BCTA 001005	L			1.0	IDC	2				1	1	12	
BCTA 001006	L	51		2.1	IDC	1	1			1	1	8	
BCTA 001007	R	17	1.0	1.5	IDC	2	1			1	1	10	
BCTA 001008	R	40	1.0	2.5	ILC	2				1	1	8	
BCTA 001009	L	78		1.4	IDC	3	1					8	1
BCTA 001010	R	86		2.5	IDC	3	1			1		11	3
BCTA 001011	L			3.0	IDC	2	1			1	1	13	
BCTA 001012	R	212		1.5	IDC	3	1					19	
BCTA 001013	L			2.5	IDC	3	1			1	1	21	6
BCTA 001014	R	55		1.2	IDC	2	1			1	1	9	
BCTA 001015	L	43		1.7	Mucinous	2	1			1	1	20	
BCTA 001016	L	52		3.0	ILC	2		1		1	1	16	
BCTA 001017	L	98	1.0	4.0	IDLC	3	1			1	1	26	16
BCTA 001018	L	140		3.9	ILC	2				1	1	18	
BCTA 001019	R	80		2.8	IDC	3	1			1	1	14	2
BCTA 001020	R	156		1.7	IDC	3	1					10	
BCTA 001021	R	110		2.0	IDC	3				1		18	9
BCTA 001022	L			3.0	IDC	2	1		1	1	1	14	
BCTA 001023	L	95		3.5	IDC	3	1					14	
BCTA 001024	L			2.0	ILC	2				1	1	12	

Related Presentations, Publications and Citations

Invited Presentations

1. Multicentricity of breast cancer: Whole organ analysis and clinical implications (Oral) **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mittra. at the **7th Biennial National Conference of Indian Society of Oncology and International Symposium on new perspectives in oncology in collaboration with Indo-American Cancer Congress Inc., USA.** at Lukhnow, 1 March, 1996.
2. Multicentricity of breast cancer: new findings and their clinical and biological implications. (Oral) at the **J S Vaidya**, I Mittra, M Baum. **1st Annual Meeting of the Indian Breast Group** at Tata Memorial Hospital, Bombay 2 March 1997
3. Future implications of novel imaging and biopsy techniques. As a **Faculty** at the **International Workshop: Multidisciplinary approach to breast cancer diagnosis**, Hamburg, Germany, 12-14 October 1998.
4. Novel radiotherapy techniques at the Middlesex hospital. JS Vaidya **Meyerstein Institute of Oncology Seminar**, London, 18 Feb 1999
5. Radiosurgery an innovative approach to management of early breast cancer. (45 min) JS Vaidya, **Surgical Forum** Meeting of the Department of Surgery, Norfolk and Norwich Hospital, 22 Jun 1999.
6. Novel radiotherapy techniques at the Middlesex hospital. JS Vaidya **Meyerstein Institute of Oncology Seminar for radiographers**, London, 4 August 1999.
7. Radiosurgery: an innovative approach to local treatment of breast cancer. Jayant S Vaidya. (1 hr) Invited talk at the Massachusetts General Hospital, **Harvard Medical School**, Boston, USA. 7 Sep 1999
8. Radiosurgery: an innovative approach to local treatment of breast cancer. Jayant S Vaidya. Invited discussion at the **Cleveland Clinic**, Cleveland, OH, USA, 8 Sep 1999
9. Radiosurgery: an innovative approach to local treatment of breast cancer. Jayant S Vaidya. Invited discussion at the Our Lady of Mercy Medical School, **New York**, USA, 13 Sep 1999
10. Breast Conservative Therapy- novel approaches- Targeted Intraoperative Radiotherapy. Jayant S Vaidya. (20 min) invited lecture, at the **Breast Cancer in the New Millenium** – in Nagpur, **India** 18 February 2000.
11. Gave a **live interview on Carlton Television (ITV)** on Intra-operative Radiotherapy for breast cancer, **London Today** 1.30 – 1.40pm, 8 Nov 2000.
12. Featured in the **BBC's Tomorrow's World** with interviews taken while performing surgery and intra-operative radiotherapy for breast cancer, **London**, 7.30pm, 8 November 2000
13. Targeted Intraoperative Radiotherapy- A novel approach to local treatment of breast cancer. JS Vaidya (30min) Invited lecture at the Satellite symposium by Photoelectron corporation, **23rd Annual San Antonio Breast Cancer Conference**, San Antonio, USA, 9 Dec 2000.
14. Targeted Intraoperative Radiotherapy for breast cancer- A randomised trial JS Vaidya (15min) Invited lecture, Satellite Symposium on Intraoperative

Radiotherapy **International Conference of Radiation Oncology (ICRO)**,
Melbourne, **Australia** 31 Jan 2001

15. Targeted Intraoperative Radiotherapy- A novel approach to local treatment of breast cancer. JS Vaidya (10min) Oral presentation, **International Conference of Radiation Oncology (ICRO)**, Melbourne, **Australia** 31 Jan 2001
16. **BBC** television interview at Saturday Breakfast News during Dec 2001/Jan 2002.
17. Intraoperative radiotherapy **Breast Cancer 2002**, Breakthrough breast cancer, London.**UK** 27 Feb 2002
18. Intraoperative radiotherapy for breast cancer- the UK experience at the **8th Annual Clinical Oncology Symposium**: Current concepts and developments in Intraoperative radiation oncology, New York, **USA**. 8 March 2002
19. Targeted Intraoperative radiotherapy- rationale, technique and results. **3rd European Breast Cancer Conference**. Barcelona, **Spain**, 20 March 2002
20. Targeted Intraoperative radiotherapy- rationale, technique and results. **Congress of the Portuguese Society of Radiology and Radiotherapy, Portugal** 17 May 2002
21. Targeted Intraoperative radiotherapy for early breast cancer- a randomised trial. **American Brachytherapy Society meeting**. Florida, **USA** 22 May 2002
22. Targeted Intraoperative radiotherapy-a randomised trial **4th Milan Breast Cancer Conference**, Milan, **Italy** 5 June 2002
23. Targeted Intraoperative radiotherapy-a randomised trial **5th UK breast cancer trialists meeting**, Birmingham, **UK** 17 June 2002.

Proffered Papers and Posters

24. Multicentricity of Breast Cancer: A whole organ analysis and clinical implications. (Poster) **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mitra. At the **Surgical Oncology Update** by International College of Surgeons and Tata Memorial Hospital, and was *awarded the first prize*, Bombay, 9-10 August 1995.
25. Multicentricity of Breast Cancer: A whole organ analysis and clinical implications. (Oral) **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mitra. at the **Weekly Clinical meeting** at the Tata Memorial Hospital, Bombay, 7 September, 1995.
26. Multicentricity and its influence on conservative breast cancer treatment strategy (Oral) **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mitra. at the **Hong Kong International Cancer Congress** on 19 Nov 1995.
27. Multicentricity of Breast cancer: new findings and their clinical and biological implications. (Oral) **J S Vaidya**, I Mitra, M Baum, at **Joint Meeting on Senology and 2nd International Conference of European Society of Mastology (EUSOMA)** at Florence, 21 March 1997.
28. Local Recurrence of Breast Cancer: New concepts about its biology and clinical relevance **J S Vaidya**, I Mitra, M Baum. at the Tripartite meeting of **British Oncological Association, Association of Cancer Physicians, and Royal College of Radiologists**, St Andrews, 7 July 1997
29. Local Recurrence of Breast Cancer: New concepts about its biology and clinical relevance **J S Vaidya**, I Mitra, M Baum. at the **5th Nottingham International Breast Cancer Conference**, 19 Sept 1997.
30. MRI in detection of Breast Cancer Multicentricity.(oral) **J S Vaidya**, M Douek, M Hall-Craggs, T Davidson, M Baum, I Taylor(Oral) at the **British Breast Group Meeting**. Cambridge, 31 October 1997
31. MRI in detection of Breast Cancer Multicentricity.(poster) **J S Vaidya**, M Douek, M Hall-Craggs, T Davidson, M Baum, I Taylor at **British Association of Surgical Oncologists (BASO) and British Association for Cancer Research (BACR) Conference** 27-28 November 1997.
32. Local recurrence has nothing to do with residual disease. (20 min) **J S Vaidya** at the Biennial **Presidential Conference of the British Oncological Association, Royal Society of Medicine**, 2 March 1998.
33. Radiosurgery: a novel method of treatment of early breast cancer. **JS Vaidya**, M Baum, JS Tobias, D D'Souza, , K Harte, P Mulvey, S Naidu, A Sliski, E Thompson, TR Varrichionne. **International Meeting on Whole-Body Stereotactic Radiotherapy**, Edinburgh, 19 September 1998.
34. Radiosurgery: A novel method of treatment of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TR Varricchionne. **British Breast Group Meeting**. Sheffield, UK, 9 October 1998.
35. Radiosurgery: A novel method of treatment of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TR Varricchione. **North London Cancer Network-Breast Cancer Tumour Board-Away Day**, Royal Society of Arts, London 13 November 1998.
36. Radiosurgery: A novel method of treatment of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TR Varricchione. **British Association of Surgical Oncologists**

- (BASO) Silver Jubilee Scientific Meeting**, The Royal College of Surgeons of England, London, 26-27 November 1998.
37. Use of Photon Radiosurgery System for intra-operative, pre-operative and as primary radiosurgery for breast cancer . JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione. **Breast Symposium for the Pearce Gould Visiting Professor**, London, 20 Mar 1999.
 38. Radiosurgery an innovative approach to management of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione **Charles Grant Clark Prize Seminar**, London 24 Jun 1999.- and **won the 2nd Prize**
 39. Radiosurgery an innovative approach to management of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione **BOA/BACR/ACP tripartite meeting**, Edinburgh, 12 Jul 1999
 40. Radiosurgery an innovative approach to management of early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione **6th Nottingham International Breast Cancer Conference**, Nottingham, 22-24 September 1999.
 41. Percutaneous excision biopsy and minimally invasive radiosurgery a novel approach to management of breast cancer. JS Vaidya, MA Hall-Craggs, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione **6th Nottingham International Breast Cancer Conference**, Nottingham, 22 -24 September 1999.
 42. Intra-operative radiotherapy: an Update (20 min) Breast Tumour Away Day of the **North London Cancer Network**, Barbican, London, 6 Oct 1999
 43. Radiosurgery: an innovative approach to local treatment of breast cancer. (Poster) JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson. **British Association of Surgical Oncologists Annual Scientific meeting**, Portsmouth, 21-23 November 1999.
 44. Targeted Intraoperative Radiotherapy- A novel approach to local treatment of breast cancer (Poster – 25 cases of the Pilot Study). JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson **5th Annual Multidisciplinary Symposium on Breast Diseases**, Rome, Italy, 12-16 February 2000.
 45. Targeted Intraoperative Radiotherapy- A novel approach to local treatment of breast cancer. JS Vaidya (oral presentation) at the British Association of Surgical Oncologists **BASO Annual Scientific Meeting**, Royal College of Surgeons of England, London, 28 Nov 2000
 46. *Targeted intraoperative radiotherapy* (Targit) for early breast cancer- a randomised trial. JS Vaidya, (8 min) Oral presentation, **Radiological Society of North America**, (narrated PowerPoint presentation) **Chicago**, 26-30 Nov 2001
 47. Targeted Intraoperative Radiotherapy for early breast cancer- A randomised trial JS (Poster) Vaidya, M Baum, JS Tobias, M Keshtgar, R Sainsbury, I Taylor, S Morgan, D D'Souza, K Harte, Alan Sliski, E Thomson **23rd San Antonio Breast Cancer Conference**, USA 10-13 Dec 2001

Peer-reviewed Papers

1. [Chapter 7] **Targeted Intraoperative radiotherapy (Targit)- A randomised controlled trial to compare targeted intra-operative radiotherapy with conventional post-operative radiotherapy after breast conserving surgery for women with early stage breast cancer.** **Jayant S Vaidya, Jeffrey S Tobias, Michael Baum, Joan Houghton.** The trial protocol has been accepted by the Lancet and is published on its website-in December 1999 at <http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=9920>
2. [Chapter 6] Percutaneous Minimally invasive stereotactic Primary Radiotherapy Jayant S Vaidya, Margaret Hall-Craggs, Michael Baum, Jeffrey S Tobias, Mary Falzon, Derek P D'Souza, Steve Morgan ***Lancet Oncology* 2002;3:252-253**
3. [Chapter 6] Minimally invasive therapy for the treatment of breast tumours Margaret A. Hall-Craggs and Jayant S. Vaidya ***European Journal of Radiology, Volume 42, Issue 1, April 2002, Pages 52-57***
4. [Chapter 5] Targeted Intraoperative Radiotherapy (TARGIT): an innovative method of treatment for early breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, S Morgan, M Metaxas, S Naidu, K Harte, Alan Sliski, E Thomson ***Annals of Oncology August 2001:12:1075-1080.***
5. [Chapter 4] The technique of delivering targeted Intraoperative radiotherapy (TARGIT). JS Vaidya, M Baum, JS Tobias, D D'Souza, S Morgan. ***Eur J Surg Oncol In Press (June 2002)***
6. [Chapter 3] Can magnetic resonance imaging help elucidate natural history of breast cancer multicentricity? Michael Douek, Jayant S Vaidya, Sunil R Lakhani, Margaret Hall-Craggs, Michael Baum, Irving Taylor. ***The Lancet* 14 March 1998; 351:801-802.** ,
7. [Chapter 3] Magnetic resonance imaging and breast cancer multicentricity. M Douek, **JS Vaidya**, I Taylor, M Baum ***The Lancet* 22 August 1998.352:652-653**
8. [Chapter 2] Multicentricity and recurrence of breast cancer M Baum, **J S Vaidya**, I Mitra, ***The Lancet.* 18 Jan 1997; 349: 208.**
9. [Chapter 2] Multicentricity of breast cancer: Whole organ analysis and clinical implications JS Vaidya, JJ Vyas, RF Chinoy, NH Merchant, OP Sharma, I Mitra. ***Br J Cancer.* Sept 1996; 74 (5): 820-824. *Commentary in The Lancet* 9 Nov 1996; 348: 1257-1258**
10. [Chapter 1] Clinical and Biological Implications of the Milan breast conservation trials. Jayant S Vaidya, Michael Baum [Editorial]. ***Eur J Cancer* August 1998; 34(8):1143-1144.**

Abstracts

1. Multicentricity and its influence on conservative breast cancer treatment strategy **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mittra. *In the proceedings of the Hong Kong International Cancer Congress*, November 1995.
2. Multicentricity of breast cancer: whole organ analysis and clinical implications **J S Vaidya**, J J Vyas, R F Chinoy, N M Merchant, O P Sharma, I Mittra. *In the proceedings of the 7th Biennial National Conference of Indian Society of Oncology (ISO) and International Symposium on new perspectives in oncology in collaboration with Indo-American Cancer Congress Inc. (IACCI)*, USA. March 1996.
3. Local Recurrence of Breast Cancer: New concepts about its biology and clinical relevance **J S Vaidya**, I Mittra, M Baum, *Br J Cancer July 1997 (76:suppl-1)(O03):17*
4. Local Recurrence of Breast Cancer: New concepts about its biology and clinical relevance **J S Vaidya**, I Mittra, M Baum, *The Breast August 1997;6(4):248-249*.
5. Multicentricity of breast cancer: new findings and their clinical and biological implications. **J S Vaidya**, M Baum, I Mittra, *Breast, October 1997; 6(5):325*
6. MRI in detection of breast cancer multicentricity M Douek, **J S Vaidya**, S R Lakhani, M A Hall-Craggs, M Baum, I Taylor. *Eur J Surg Oncol Dec 1997;23(6):591*
7. Preoperative MRI does not influence the amount of breast tissue excised in conservative cancer surgery M Douek, **JS Vaidya**, T Davidson, SR Lakhani, MA Hall-Craggs, M Baum, I Taylor. *Eur J Cancer 1998;34(S5): p.189*
8. Detection of breast cancer multicentricity with MRI. M Douek, **J Vaidya**, T Davidson, SR Lakhani, MA Hall-Craggs, K Blanchard, M Baum, I Taylor. *Anticancer Res 1998;18:3837*
9. MRI currently does not influence the amount of breast tissue excised in conservative cancer surgery M Douek, **JS Vaidya**, T Davidson, SR Lakhani, MA Hall-Craggs, M Baum, I Taylor. *Anticancer Res 1998;18:3838*
10. Radiosurgery: A novel method of treatment of early breast cancer. **JS Vaidya**, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione. *Eur J Surg Oncol. 1998;24(6):619*.
11. MRI in the detection of breast cancer multicentricity AU: Douek M, **Vaidya J**, Lakhani SR, Blanchard K, Hall-Craggs MA, Davidson T, Baum M, Taylor I *Br J Surgery, 1998, Vol.85, No.S1, p.66 (2)*
12. Pre-operative detection of breast cancer multicentricity with MRI Douek_M, **Vaidya_J**, Davidson_T, Lakhani_SR, HallCrag_MA, Blanchard_K, Baum_M, Taylor_I *Eur J Cancer, 1998, Vol.34, No.S5, P.319 (3)*
13. Radiosurgery: An innovative method of local treatment of breast cancer. . **JS Vaidya**, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson, TRVarricchione. *Br J Cancer. 1999; July 1999;80:(Suppl6-P285):100*
14. Targeted intraoperative Radiotherapy-(Targit) A novel approach to local treatment of early breast cancer. **JS Vaidya**, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, P Mulvey, Alan Sliski, E Thomson *The Breast Journal Sep/Oct 2000 Vol 6(5):339*
15. Targeted intraoperative Radiotherapy-(Targit) A novel approach to local treatment of breast cancer. **JS Vaidya**, M Baum, JS Tobias, D D'Souza, K Harte, , S Naidu, S Morgan, Alan Sliski, E Thomson *European Journal of Surgical Oncology Dec 2000;26(8): 862*

16. Targeted intraoperative Radiotherapy (Targit): A novel approach to local treatment of breast cancer. JS Vaidya, M Baum, JS Tobias, D D'Souza, K Harte, S Naidu, S Morgan, M Metaxas Alan Sliski, E Thomson *Radiotherapy & Oncology Jan 2001;58(suppl 1):S10-31*
17. Targeted intraoperative Radiotherapy: an innovative method of treatment for early breast cancer. JS Vaidya, M Baum, JS Tobias, S. Morgan, E Thomson *European Journal of Cancer 2001;37(suppl 2):S84-85*
18. Targeted intraoperative radiotherapy (Targit) for early breast cancer- a randomised trial. JS Vaidya, M Baum, JS Tobias, J Houghton, M Keshtgar, R Sainsbury, I Taylor, D D'Souza, S. Morgan, M Metaxas, K Harte, A Sliski, E Thomson *European Journal of Cancer 2001;37(suppl 5):37.*
19. Percutaneous Minimally Invasive Stereotactic Primary Radiotherapy: A Novel Approach For Breast Cancer In Elderly Women Vaidya JS, Hall-Craggs MA, Baum M, Tobias JS, Keshtgar M, Sainsbury R, Taylor I, D'Souza DP, Naidu SV, Morgan S, M Metaxas, Harte KJ, Sliski AP, Thomson E. *Eur J Cancer 2001;37(suppl 5):37-38.*
20. Targeted intra-operative radiotherapy (TARGIT) for breast cancer: A randomised trial Vaidya JS, Tobias JS, Baum M, Houghton J, Keshtgar M, Sainsbury R *Radiology 221: 278-278, Suppl. S NOV 2001*
21. Targeted intraoperative radiotherapy for breast cancer - a randomised trial. Vaidya JS, Baum M, Tobias JS, Houghton J, Keshtgar M, Sainsbury R, Taylor I, Morgan S, Metaxas M, D'Souza D *Breast Cancer Research And Treatment 69 (3): 145 2001*
22. Targeted intraoperative radiotherapy (Targit) for early breast cancer- Rationale and early clinical experience. JS Vaidya, M Baum, JS Tobias, J Houghton, M Keshtgar, R Sainsbury, I Taylor, D D'Souza, M Metaxas, S. Morgan, , K Harte, A Sliski, E Thomson *European Journal of Cancer 2002;38(suppl 3):S89-S90.*
23. Targeted intraoperative Radiotherapy for breast cancer: An international Trial J S Vaidya, D Joseph*, B S Hilaris**, J S Tobias, J Houghton, M Keshtgar, R Sainsbury, I Taylor, M Baum. Submitted to *Radiother. Oncol.* For ESTRO 2002

Citations

1. Multicentricity of breast cancer: whole-organ analysis and clinical implications. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mitra I **Br J Cancer** 1996 Sep;74(5):820-824
 - 1.1. Multicentricity and Recurrence Of Breast-Cancer Sacchini_V **Lancet**, 1996, Vol.348, No.9037, Pp.1256-1257
 - 1.2. Multicentricity and recurrence of breast cancer - Reply Sacchini_V **Lancet**, 1997, Vol.349, No.9046, p.208
 - 1.3. Perioperative stimulation of residual cancer cells promotes local and distant recurrence of breast cancer Reid_SE, Kaufman_MW, Murthy_S, Scanlon_EF **Journal Of The American College Of Surgeons**, 1997, Vol.185, No.3, pp.290-306:
 - 1.4. Does preoperative MRI influence the extent of surgical resection in conservative breast cancer surgery? Douek_M, Davidson_T, HallCraggs_MA, Lakhani_SR, Baum_M, Taylor_I **Breast**, 1999, Vol.8, No.2:.84-88
 - 1.5. Preoperative MR mammography for breast cancer - impact on planning of operative treatment Gatzemeier_W, Liersch_T, Stylianou_A, Buttler_A, Becker_H, Fischer_U **Chirurg**, 1999;70(12): 1460-68
 - 1.6. Impact of multicentricity on clinical outcome in patients with T1-2, N0-1, M0 breast cancer Vlastos G, Rubio IT, Mirza NQ, et al. **Ann Surg Oncol** 7: (8) 581-587 SEP 2000
 - 1.7. Breast carcinomas of limited extent - Frequency, radiologic-pathologic characteristics, and surgical margin requirements Faverly DRG, Hendriks JHCL, Holland R **Cancer** 91: (4) 647-659 FEB 15 2001
 - 1.8. Gennaro M, Ferraris C, Guida V, et al. Conservative surgery in breast cancer. Significance of resection margins **Breast** 10 (5): 432-437 OCT 2001
 - 1.9. Andea AA, Wallis T, Newman LA, et al. Pathologic analysis of tumor size and lymph node status in multifocal/multicentric breast carcinoma **Cancer** 94 (5): 1383-1390 MAR 1 2002
 - 1.10. Multicentric mammary carcinoma - Evidence of monoclonal proliferation Middleton LP, Vlastos G, Mirza NQ, Singletary SE, Sahin AA **Cancer** 94 (7): 1910-1916 APR 1 2002
2. Multicentricity and recurrence of breast cancer M Baum, J S Vaidya, I Mitra, **The Lancet**. 18 Jan 1997; 349: 208
 - 2.1. Does preoperative MRI influence the extent of surgical resection in conservative breast cancer surgery? Douek_M, Davidson_T, HallCraggs_MA, Lakhani_SR, Baum_M, Taylor_I **Breast**, 1999, Vol.8, No.2:.84-88
 - 2.2. Subclinical disease revisited Kagan AR, Morgan TL **Am J Clin Oncol-Canc** Dec 1999 22: (6) 621-626
3. Can MRI be used to elucidate the natural history of breast cancer multicentricity? Michael Douek, Jayant S Vaidya, Sunil R Lakhani, Margaret Hall-Craggs, Michael Baum, Irving Taylor. **The Lancet** 14 March 1998;351:801-802.
 - 3.1. Magnetic-resonance imaging in breast cancer Boggis_CRM, Bundred_NJ **Lancet**, May 1998, 351, No.9112, p.1362
 - 3.2. Magnetic-resonance imaging for breast cancer Drew_PJ, Turnbull_LW, Kerin_MJ **Lancet**, 1998, Vol.351, No.9116, pp.1661-1662
 - 3.3. Magnetic-resonance imaging and breast cancer multicentricity - reply Drew_PJ, Turnbull_LW, Kerin_MJ **Lancet**, 1998, Vol.352, No.9128, p.653

- 3.4. Does preoperative MRI influence the extent of surgical resection in conservative breast cancer surgery? Douek_M, Davidson_T, HallCraggs_MA, Lakhani_SR, Baum_M, Taylor_I **Breast**, Apr 1999, Vol.8, No.2, pp.84-88
- 3.5. Dynamic contrast enhanced Magnetic Resonance Imaging of the breast is superior to triple assessment for the pre-operative detection of multifocal breast cancer Drew_PJ, Chatterjee_S, Turnbull_LW, Read_J, Carleton_PJ, Fox_JN, Monson_JRT, Kerin_MJ **Annals Of Surgical Oncology**, Sep 1999, Vol.6, No.6, pp.599-603
- 3.6. Prospective comparison of standard triple assessment and dynamic magnetic resonance imaging of the breast for the evaluation of symptomatic breast lesions Drew_PJ, Turnbull_LW, Chatterjee_S, Read_J, Carleton_PJ, Fox_JN, Monson_JRT, Kerin_MJ **Annals Of Surgery**, Nov 1999, Vol.230, No.5, pp.680-685
- 3.7. Genetic alterations in 'normal' luminal and myoepithelial cells of the breast. Lakhani_SR, Chaggar_R, Davies_S, Jones_C, Collins_N, Odel_C, Stratton_MR, OHare_MJ **Journal Of Pathology**, 1999, Vol.189, No.4, pp.496-503
- 3.8. MRI contribution to the diagnosis of breast disease Tardif-de Gery S, Zagdanski AM, Merzoug V, et al. **Presse Med** 29: (20) 1145-1153 JUN 10 2000
4. Magnetic-resonance imaging and breast cancer multicentricity Douek M, Vaidya JS, Baum M, Taylor I **The Lancet** 352: (9128) 652-653 AUG 22 1998
- 4.1. MRI contribution to the diagnosis of breast disease Tardif-de Gery S, Zagdanski AM, Merzoug V, et al. **Presse Med** 29: (20) 1145-1153 JUN 10 2000
5. Clinical and Biological Implications of the Milan breast conservation trials. Jayant S Vaidya, Michael Baum [Editorial]. **Eur J Cancer** August 1998; 34(8):1143-1144
- 5.1. The natural history of breast cancer Jatoi_I **Surgical Clinics Of North America**, 1999, Vol.79, No.5, p.949 (13 pages)

Cited and quoted in cover story- 'The new thinking on breast cancer- the smartest drugs, the gentlest treatments, the latest on mammograms' **Time Magazine** (European Edition) 10 June 2002, p 52.