A NOVEL APPROACH FOR LOCAL TREATMENT OF BREAST CANCER

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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DEDICATED TO

MY FATHER

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AND

MY MOTHER

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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 examinst 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 Gallenic 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 or 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 square = 30.6, P < 0.001). There were significantly more distant relapse in the latter group (chi square = 6.32, P = 0.01), and a significant increase in breast cancer deaths (57% versus 44%,;chi square = 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

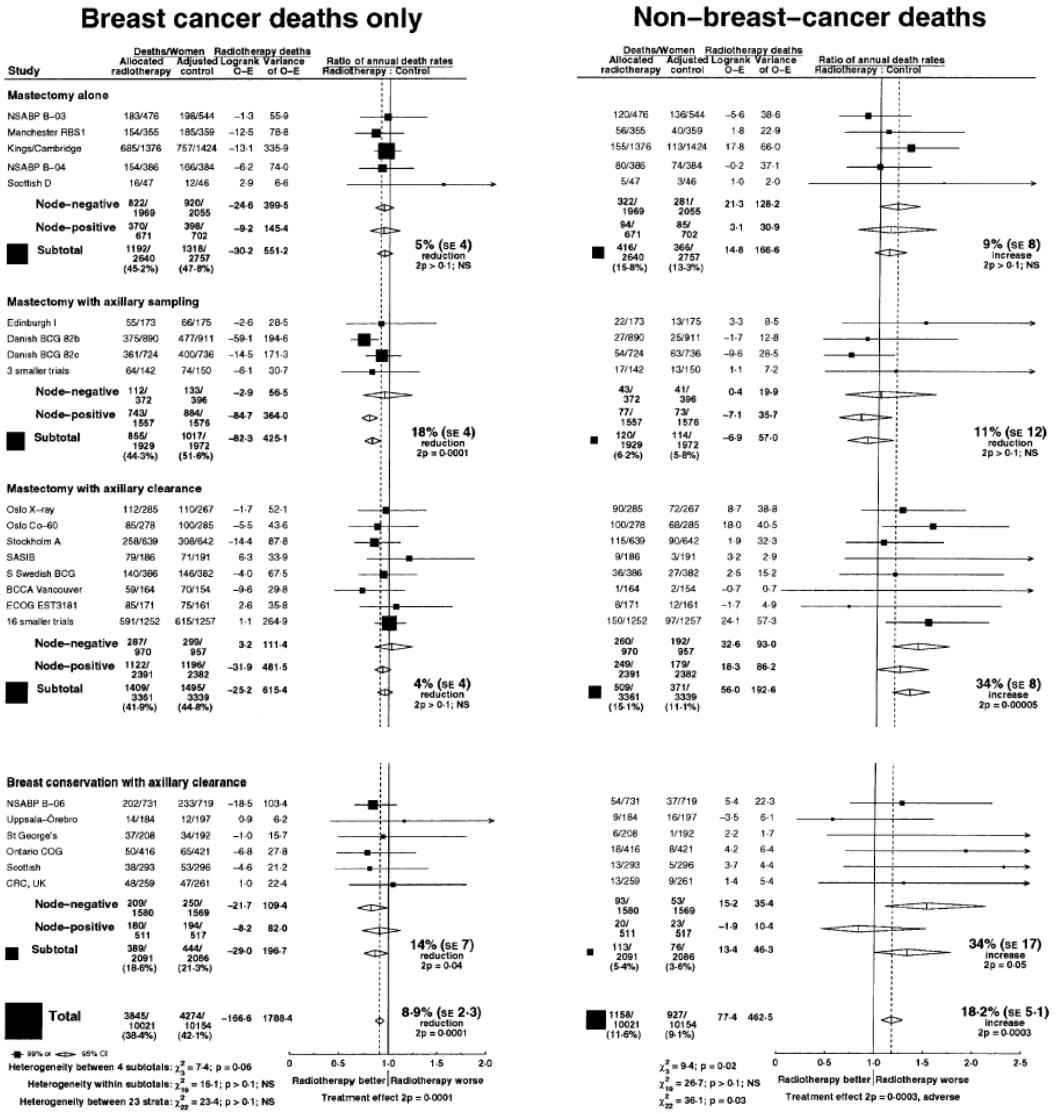
patient data and included 40 published and unpublished trials [Early Breast Cancer Trialists' Collaborative Group, 2000] with special attention to the Danish trials. This meta-analysis (see figure) showed that radiotherapy reduced the local recurrence from 27.2% to 8.8% at 10 years. Breast cancer mortality 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!

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.

<u>The CRC trial</u>

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 there groups. But, after adjustment for fixed co-variates 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), dose (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 heterozygocity, 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 harbinger 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].