A NOVEL APPROACH FOR LOCAL TREATMENT OF BREAST CANCER

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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1996-2001

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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 or 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)

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).

Institution	Radio-therapy tech-nique	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;

Title of the trial

*TARGIT- TARG*eted *I*ntraoperative radio*T*herapy 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 (Targit) – 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.

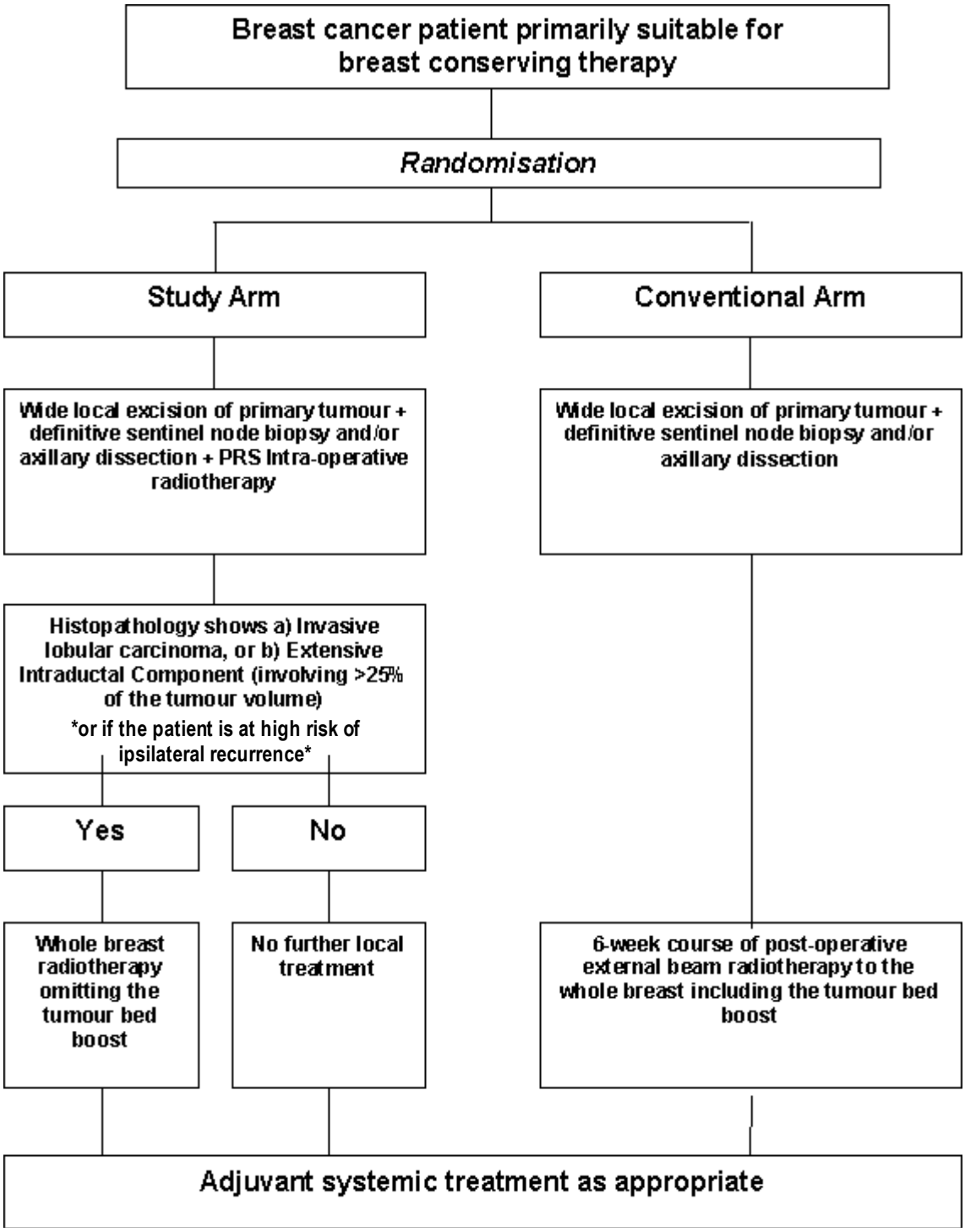
Patient satisfaction

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 his 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 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 x 27000 x 3750) per year for the NHS. *In addition,* the saving of expensive resource time on linear accelerators would of course be substantial.