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Radiotherapy or Tamoxifen after Conserving Surgery for Breast Cancers of Excellent Prognosis: BASO II TRIAL

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ABSTRACT

Background. The incidence of local recurrence (LR) after conservative surgery for early breast cancer without adjuvant therapy is unacceptably high even with favourable tumours. The aim of this study was to examine the effect of adjuvant therapies in tumours with excellent prognostic features.

Methods. Patients with primary invasive breast cancer <2cm diameter, grade 1 or good prognosis special type, and node negative, treated by wide local excision (WLE) with clear margins were randomised into a 2X2 clinical trial of factorial design with or without radiotherapy and with or without tamoxifen. Trial entry was allowed to either comparison or both.

Findings. The actuarial breast cancer specific survival in 1135 randomised patients at 10 years was 96%. Randomisation by intention to treat showed that LR after WLE alone was 1.9% per annum vs 0.7% with radiotherapy alone ($p<0.001$, HR 0.37, CI 0.22-0.61) and 0.8% with tamoxifen alone ($p<0.004$, HR 0.33, CI 0.15-0.70). No patient randomised to both adjuvant treatments developed LR. Analysis by treatment received showed LR at 2.2% pa. for surgery alone vs 0.8% for either adjuvant radiotherapy or tamoxifen and 0.2% for both treatments.

Conclusions. Even in these patients with tumours of excellent prognosis, LR after conservative surgery without adjuvant therapy was still very high. This was reduced to a similar extent by either radiotherapy or tamoxifen but to a greater extent by the receipt of both treatments.

Keywords: Randomised clinical trial; breast cancer; radiotherapy; tamoxifen; prognosis; local recurrence.

INTRODUCTION

Previous studies [1-8] have all shown a marked reduction from the application of radiotherapy (RT) to the risk of local recurrence (LR) following breast-conserving surgery. Although the overall absolute risk level without RT has been reported as high as 20% - 40%, this still means that the majority do not suffer LR. The BASO II trial was an attempt to identify a group in which the absolute risk of LR is low enough to omit treatment with RT, and to compare the effects on LR of adjuvant tamoxifen with RT. Thus the trial tested (i) no added treatment, (ii) addition of intact breast irradiation (RT), (iii) addition of adjuvant tamoxifen and (iv) application of both treatments, following wide local excision (WLE) in a group of patients with excellent prognosis breast cancer.

The Nottingham Prognostic Index (NPI) places cases into groups with significantly differing prognoses[9]. The Excellent Prognostic Group (EPG), with a 96% survival at 10 years (without adjuvant systemic therapy), represents primary invasive breast cancers of the least aggressive potential and this was the group chosen for inclusion in the trial. Specifically it is composed of invasive breast cancers that are grade 1, with negative lymph nodes (LN) in the axilla and are 2 cm or less on microscopic measurement of maximum dimension. Over 90% of these tumours are oestrogen receptor (ER) positive[10]. For the trial, to these cases were added certain special types (usually graded as 1 in any case), of the same negative LN status and small size.

PATIENTS AND METHODS

Trial entry

Each centre wishing to enter data was required to obtain local ethics committee approval and to send confirmation of this to the Data Centre and to the Randomisation Units. For entry, all cases had to have undergone wide local excision (WLE) and to have had a pathology report indicating that the margins of the operative specimen were clear of tumour microscopically. The pathology reports outlining were reviewed for confirmation of suitability for trial entry.

Eligibility included women under 70 years of age with primary operable unilateral invasive breast cancer with no evidence of metastases. Surgical therapy was WLE, with the margins of excision clear of both invasive breast cancer and ductal carcinoma *in situ* (DCIS). The invasive carcinomas had to be of histological grade 1 or specific good prognosis special types (tubular, cribriform, tubular/cribriform, papillary or mucinous). Tumours had to be of maximum diameter 20mm or less and have no evidence of lympho-vascular invasion (LVI). Histological examination of lymph nodes, excised by sampling or dissection, had to be negative.

Additionally, ineligible were patients with DCIS and microinvasive carcinoma alone, those with Paget's disease of the nipple, patients with synchronous bilateral breast cancer, those with a previous diagnosis of any cancer other than adequately treated basal cell carcinoma of the skin, and pregnant or lactating women. Also excluded were those women with evidence of distant metastases and those with other diseases that might preclude adequate surgery, adjuvant therapy or follow-up. Similarly those with planned receipt of any adjuvant therapy other than those within the trial were ineligible for trial entry.

The randomised clinical trial was structured as a 2 x 2 factorial design (Figure 1) so as to compare the effects of added RT, or of added tamoxifen, or both. Prior to entering, each centre was required to select one of the following options:

Option 1:   Entry to all four arms: WLE only, WLE + RT, WLE + tamoxifen, WLE + RT + tamoxifen (i.e. treatment entirely according to randomisation).

Option 2:   Entry to WLE only vs WLE + tamoxifen (i.e. centre choice not to use RT).

Option 3:   Entry to WLE only vs WLE + RT (i.e. centre choice not to use tamoxifen).

Option 4:   Entry to WLE + tamoxifen vs WLE + tamoxifen + RT (i.e. centre choice for all to receive tamoxifen).

Option 5:   Entry to WLE + RT vs WLE + RT + tamoxifen (i.e. centre choice for all to receive RT).

Thus some centres opted to randomise patients to all 4 arms (Option 1). Others units, for example, wished all the eligible patients to received tamoxifen and so they selected to randomise to WLE with and without RT (with patients in both arms in that Unit receiving tamoxifen; Option 4).

Informed consent was obtained after post-operative receipt of the histological report. The patient was given an information sheet explaining the excellent prognosis of her cancer and the aims of the trial and then was able to discuss the trial with the surgeon or radiotherapist, and the breast care nurse. In 1992 there was no formal requirement for patients to sign a consent form although this was a requirement in the revised protocol of 1995.

Randomisation was carried out at the time consent was obtained, by telephone at one of two centres: Scottish Cancer Trials Unit, Edinburgh and Cancer Research Campaign (CRC) Trials Centre, London. Further patient information sheets for the tamoxifen and radiotherapy options, and on the possible side-effects, were given to patients according to their randomisation. The Breast Unit and the patient's General Practitioner (GP) were advised of the randomisation and the GP was asked to prescribe, or not to prescribe, tamoxifen.

Initial data collected on entry included the patient's date of birth and confirmation of the surgical procedure and histopathological features by review of the surgical excision pathology report. The histopathology data collected included the histological grade and subtype, presence or absence of lympho-vascular invasion (LVI) and invasive carcinoma size. The histology report was also reviewed for confirmation that margins of the operative specimen were clear of tumour and that lymph nodes were negative. All data were entered onto a standard form and entered into the trial database at the Data Centre at Nottingham City Hospital.

Follow-up

The minimum requirement was for annual follow-up, for the recording of which trial forms were to be returned to the Data Centre. The suggested schedule was 3 monthly for 2 years and 6 monthly thereafter. Annual mammography of the treated breast was recommended. According to national guidelines, however, since 2007, many hospitals reduced follow-up. 73% of subjects were followed up at least to 2007.

Date last known to be alive without recurrence, or diagnosis and dates of local, regional or distant recurrence or of death, were notified to the Data Centre. Any diagnosis of contralateral breast cancer was also recorded, as was the diagnosis of any other cancer. Local recurrence (LR) was defined as further invasive carcinoma or DCIS in the skin or soft tissues, within a defined ipsilateral anatomical area (clavicle, mid-sternum, costal margin, posterior axilla). Differentiation into true LR or new primary breast cancer was not attempted. Regional recurrence (RR) was defined as nodal involvement in the axilla or internal mammary chain. For local or regional recurrence, histological or cytological confirmation was required. For systemic recurrence one of the following was required: histological diagnosis, radiological lesion diagnostically not in doubt, progression of a lesion (clinical or radiological).

Data updates were requested for patients without recent information, at three yearly calls from the data centre. The following events were recorded (with the date of their first diagnosis): LR, RR, contralateral breast cancer, distant metastases (DM) and death, and whether breast cancer specific. If a patient had been diagnosed with distant metastases, even if apparently in remission at time of death, death was classified as 'with breast cancer'. If no diagnosis of distant metastases had been made (even following any prior LR or RR controlled at time of death by surgery or RT), this was classified as 'without known active breast cancer'. Events were reported to the central data manager, who then re-checked the histology or cause of death with the reporting centre.

Sample size and recruitment

With LR as the main endpoint and with anticipated rates of LR of 1% per annum (PA) relapse rate with extra therapy and 2% PA rate without any extra therapy, the trial aimed to recruit a minimum of 600 cases for each of the main effects analyses of either RT or tamoxifen (300 with treatment, 300 without), with a 90% chance of detecting a difference of 10% at 10 years.

Recruitment was excellent to the RT vs no RT randomised comparison (558 vs 557), but did not reach the anticipated goal for the tamoxifen vs no tamoxifen comparison (213 vs 213). 1171 cases in total were entered between 04.02.1992 and 28.10.2000.

Treatment

Surgery

Patients had to have undergone wide local excision (WLE). WLE was defined in the trial protocol as surgical removal of the tumour mass with an intended minimum width of $0.5 - 1.0$ cm of surrounding uninvolved tissue; very wide excision, such as by quadrantectomy/segmentectomy was not intended. The margins of the excised specimen had to be judged clear of tumour on histological examination (if necessary, after a re-excision). For tumours extending up to, but not through, the pectoral fascia or up to the superficial surface of the breast without involvement of the dermis, re-excision was not mandatory.

Either axillary node sampling or clearance (low or full) had to have been performed. It should be noted that the trial accrual took place prior to the widespread use of the sentinel lymph node

technique. For sampling, one node was stated to be sufficient, although four nodes were preferred.

Adjuvant Therapies

The tested adjuvant therapies were intact breast irradiation (RT) and tamoxifen.

Radiotherapy Option

Radiotherapy was prescribed according to randomisation and to those receiving RT by elective choice of the Unit (see 'randomisation' above). Whole breast irradiation was given with fractionation in the range between 40 Gy in 15 fractions and 50 Gy in 25 fractions. A boost to the tumour bed was recommended, but not obligatory. The lymph node drainage areas were not irradiated (node positivity excluded patients from trial entry).

Tamoxifen Option

Tamoxifen 20 mg daily for 5 years was prescribed to women randomised to tamoxifen and to those receiving tamoxifen by the elective choice of the Unit.

Pathology

Pathological specimen handling and histological examination was carried out according to the criteria laid down in 'Pathology Reporting in Breast Cancer Screening'[11]. The findings were recorded on the National Breast Screening Pathology form. Tumours had to be graded[12] and typed[13]. Thorough examination of the margins of the excision was mandatory (see 'Surgery').

Analysis

Analysis was performed first by randomisation (intention to treat) and then by treatment received. Data were analysed by Cox proportional hazards regression, complemented by tabulation of numbers of LR cases observed, and annual rates of LR. Data were analysed using STATA version 10.

The total number of patients randomised was 1171. Thirty-one patients changed their mind after randomisation, but before treatment. They were included in 'intention to treat' analysis according to their randomisation as well as in the analysis by 'treatment received'. Thirty-six were withdrawn as they were later found to have ineligible entry criteria, leaving 1135 for the analyses.

RESULTS

The median time from entry to the trial to last individual follow-up in August 2011 was 167 months (range 130-234). The median observation time was 121 months. Mean age at trial entry was 57 years (range 33 − 69). In total, 1135 patients were randomised and included in analysis (Figure 1). As shown in Figure 1, a total of 557 (356+95+106) were randomised to no RT, 558 (353+107+98) to RT, 213 to no tamoxifen and 213 to tamoxifen. A total of 406 (95+107+106+98) were randomised in the full 2 x 2 factorial design.

Survival and distant metastases

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At final follow-up, there have been 49 deaths with or from breast cancer (0.46% PA), compared with 68 deaths from other causes. A further 7 patients have been diagnosed with distant metastases. Overall ten-year survival was 96%. Both RT and tamoxifen were associated with non-significant improvements in survival (data available but not presented).

Local Recurrence

In total 83 patients suffered LR. Table 1 shows the intention to treat effects of RT vs no RT and of tamoxifen vs no tamoxifen. All cases randomised in all options are included. Thus in the comparison of RT vs no RT some cases on either side may have received tamoxifen and similarly in the comparison of tamoxifen vs no tamoxifen cases may have received RT.

Additional effect of Radiotherapy

Available for this analysis were all cases entered into option 1 (i.e. entry to all four arms); to option 3 (WLE vs WLE+RT; when the centre elected not to give tamoxifen to any case) and to option 4 (WLE+tamoxifen vs WLE+ tamoxifen+RT; when it was the choice of the unit that tamoxifen was given to all cases). Fifty-seven of 557 (10.2%) women who did not receive RT suffered LR compared to 22 of 558 (3.9%) who had RT. The result shows a highly significant (p < 0.001) advantage to the use of RT in avoiding LR, with a Cox regression hazard ratio (HR) of 0.37 (95% CI 0.22-0.61).

Additional effect of tamoxifen

Available were those cases entered in option 1 (entry to all four arms), option 2 (WLE vs WLE+tamoxifen; where the centre elected not to give RT to any case) and option 5 (WLE vs

WLE+tamoxifen; where the centre chose RT for all cases). Overall, 25 of 213 (11.7%) patients who did not receive adjuvant tamoxifen suffered LR, compared to 9 of 213 (4.2%) who were randomised to tamoxifen. Again a significant advantage in avoiding LR is seen to the prescription of tamoxifen (p=0.004), with a HR of 0.33 (95% CI 0.15-0.70).

Combined effects and comparison of all 4 arms

The results of the four-way comparison from cases randomised in option 1 (i.e. only from Units entering patients into all 4 arms of the trial) were analysed to assess differences between those receiving neither additional therapy vs both (Table 2). This allows comparison of the addition of RT only, and the addition of tamoxifen only, as well as the use of both therapies over the use of only RT or only tamoxifen. The absolute LR rates are also noteworthy here, since the LR rates for the addition of RT, or tamoxifen, are not complicated by the receipt of the alternative therapy in some patients. As one would expect, receiving both therapies was highly significantly protective of LR (p<0.001), with 15 of 95 patients receiving neither treatment suffering LR (1.9% per year) whilst none of the 98 (0%) women randomised to receive both treatments experienced LR. Tamoxifen had a significant protective effect after adjustment for RT (p=0.003) and vice versa (p=0.002). Receipt of both therapies conferred a significantly lower risk of LR than RT alone (p=0.01) and also a significantly lower risk than use of tamoxifen alone (p=0.006).

Analysis by Treatment Received

The results for the randomised comparison of both treatments simultaneously are in broad agreement with the outcomes by treatment actually received. Figure 2 shows LR-free survival by

the four treatment combinations received. The receipt of neither therapy gave an average annual LR rate of 2.2%; RT alone gave 0.8%; tamoxifen alone gave 0.8%; and both RT and tamoxifen gave an annual LR rate of 0.2%. Significant reductions in risk of LR were observed with receipt of RT (HR = 0.36, 95% CI 0.19-0.67, p=0.001) and tamoxifen (HR = 0.35, 95% CI 0.21-0.58, p<0.001). The LR rates did not differ significantly between the two single therapies (p=0.90). Receipt of both therapies was significantly associated with lower LR rates than receipt of either alone (p=0.005 for tamoxifen in addition to RT; p=0.002 for RT in addition to tamoxifen).

Contralateral breast cancer

27 contralateral breast cancers have been reported (one DCIS), a rate of approximately 2.6 per 1000 women-years. Of those actually receiving tamoxifen, 1.5% had a contralateral breast cancer, compared to 4.5% of those not receiving tamoxifen. There was no difference in the rate of contralateral breast cancer with respect to receipt of RT.

DISCUSSION

The randomised comparison between the receipt of RT vs no RT in this group of women with completely local excised invasive breast cancers shows that RT confers a highly significant reduction in the risk of LR, entirely in line with previous reports. However, the primary question addressed by this study was whether the absolute rate of LR could be sufficiently low (<1% PA) to be clinically applicable when RT was omitted in this selected group of patients with tumours of excellent prognosis (both predicted and confirmed). The analyses by randomisation show a highly significant advantage to the use of either therapy, and further advantage to the use of both. The analysis by treatment received shows an unsatisfactory rate of LR when RT is omitted with

no other adjuvant therapy, but that a less severe rate of 0.7% PA is achieved when RT or the alternative of tamoxifen therapy is used. Although this was not an equivalence trial, the results give convincing evidence that tamoxifen can safely be used as an alternative to RT in this patient group. An extremely low rate of LR was achieved by the use of RT plus tamoxifen. Indeed no cases were observed in those randomised to receive both treatments, and only 7 out of the 374 patients who actually received both treatments (0.2% PA). Secondary analyses, for treatment actually received, for breast cancer specific survival, and for any breast event were all consistent with the primary results (data available from the authors).

The question of whether intact breast irradiation is necessary after breast conserving surgery has been addressed in clinical trials dating back to the 1980's. Early trials evaluated the efficacy of extensive excision (quadrantectomy) with and without irradiation, and showed a considerable benefit to receipt of RT[2]. Subsequent trials[3, 4] compared less extensive surgery with and without RT, and similarly showed a significant advantage to the RT arm.

Others, therefore, attempted to specifically select for investigation those cases likely to be at lower risk of LR. In general these have included smaller tumours and node negative disease with widely tumour-free margins. The Boston (USA) group reported the outcome of 87 patients not receiving adjuvant RT or systemic therapy (mean age 67; tumours $\leq$ 2 cm; ductal/ no special type, tubular or mucinous carcinomas; node negative, clear margin of at least 1 cm)[5]. At a median follow-up of 56 months an average annual recurrence rate of 3.6% per annum was reported. The Uppsala-Orebro trial[6] randomised 381 women with tumours of maximum mammographic size of 2 cm, node negative and tumour-free margins to a 20 mm width. At

around 30 months of follow up the actuarial LR rates were 2.9% in the group treated with RT and 7.6% in the group without RT. A Finnish trial[7] evaluated the addition of RT in 152 patients with favourable features (patients >40 years, tumours <2 cm, grade 1 or 2, progesterone receptor positive) following WLE with a minimum of 1 cm tumour-free margin. Again no patient received systemic adjuvant therapy and at a mean of 6.7 years distant metastases had occurred in 5.9%, confirming the generally good prognosis, but LR rates were 18.1% without RT and 7.5% with RT. Similarly, the German Breast Cancer Study Group (GBSG)[8] entered 347 women (≤ 2 cm tumours, node negative, grade 1 or 2 and ER positive) into a trial randomising to RT (yes/no) and/or 2 years tamoxifen (yes/no) in a 2 x 2 factorial design. At a median of 5.9 years LR was three times higher in the group with WLE alone than in the other three groups. Finally, the NSABP B-21 trial of RT, tamoxifen or both, after WLE of tumours $\leq$1cm reported LR at 8 years of 9.3%, 16.5% and 2.8% respectively[14].

Thus none of the previous trials of RT and WLE have satisfactorily identified a group of patients who have a very low risk of LR and, in practical terms, to whom most Units would feel it appropriate not to offer RT after WLE. In essence, these previous trials have selected groups of patients with good prognosis based on clinical and histological features, but have not included only those women with the very best predicted outcome. The present, BASO II, trial selected cases with a Nottingham Prognostic Index (NPI)[9] score of $\leq$ 2.4 (Excellent Prognostic Group), i.e. those of lowest natural inherent aggressiveness (grade 1), earliest in progression (small and node negative) and most likely to respond to hormone manipulation. The oestrogen receptor (ER) status was not available but this is likely to have been positive in over 90% cases since the Oncopool study showed that 91% grade 1 tumours were ER positive[10].

Although nodal assessment in this trial was not determined as per present day standards (axillary node sampling or clearance was performed) this is unlikely to have any significant influence on the trial results per se. Patients identified as node negative by SLN have a better outcome than those defined as node negative by node clearance[15] and one might be even more certain that a patient had an excellent prognosis with more modern modes of nodal examination. Despite this, that the patients included in the trial had an excellent prognostic assessment was borne out by the 10-year breast cancer specific actuarial survival of 96%; the level predicted by the NPI for the excellent prognosis group. All cases also had clear margins of excision on histology and other known risk factors for LR, such as the presence of lympho-vascular invasion, were also excluded. Since these tumours were frequently detected by the UK NHS mammographic screening programme, most patients were over the age of 50 years so the other known factor of young age as risk for LR[16] rarely applied. The group of patients selected for inclusion in this trial therefore is that with the best possible prognostic factors and an absence of features known to reflect an increased risk of LR.

The randomised comparison showed in the first 10 years of follow-up that the well recognised relative risk reduction of LR achieved by post-operative RT was also seen in this selected group. In addition it showed that systemic tamoxifen therapy gave equal local control in these excellent prognosis, and (from the literature) largely ER positive[10], tumours to that achieved by radiotherapy. Finally we report that LR was very unusual in cases given both therapies. The analysis of BASO II by treatment received is essentially an observational study of the absolute levels of LR achieved by the treatments in this large and well-defined sub-group of women with

excellent prognosis tumours undergoing breast conserving therapy, rather than the randomised comparison of treatments. As such it would seem of greater relevance to the clinician. This analysis by treatment received shows actuarial rates of LR at 10 years of 22% without either adjuvant therapy, 8% for the addition of RT alone, 8% for the addition of tamoxifen and 2% when both treatments were applied to this relatively small group of patients with strictly selected prognostic factors.

As with the studies examining the benefit of RT, series assessing the role of tamoxifen in influencing LR have not selected for inclusion only those women with the very best predicted outcome. Subgroup analysis of the Scottish Trial[3] (tumours of up to 4 cm and node positive cases) showed little effect on LR from tamoxifen. In a Canadian trial[17] of ER positive tumours (2 cm or less, node negative, but including grade 3 lesions), all of who received tamoxifen, the LR rate at 8 years was 3.6% with RT and tamoxifen vs 15.2% in women treated without RT but with tamoxifen. However, in a planned subgroup analysis of 611 women aged 50 or over, with node negative and ER positive tumours of 1 cm or less, the 5 year local relapse rates were 5.9% with tamoxifen alone and 0.4% with tamoxifen + RT. The effect of tamoxifen in terms of estimated relative risk reduction in the present trial is higher than that reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview[18] but again it is relevant that the patients included in the present study are only those of excellent prognosis. Although ER status is not available in this series, it is highly likely that the vast majority have strongly ER positive disease (given that they are grade 1 or defined special type) and it is likely that tamoxifen may be particularly effective in this group. In both this (BASO II) and the GBSG trials[8] of tumours with good prognoses, LR was reduced to one third of the level seen in women

given neither tamoxifen nor RT. Similarly, in the present trial, LR reaches negligible levels by the application of both, as in the Canadian trial[17].

The incidence of contralateral breast cancers is lower than one might anticipate from the EBCTCG meta-analysis, which at 10 years showed a rate of 3.9% with tamoxifen and 7.2% without[18]. Although this may reflect issues in long term collection of this follow-up data it is also likely to be the case that this has been influenced by receipt of tamoxifen, as a result of policy or randomisation, and potentially the nature of the tumours in the group of women with very low risk invasive breast cancer.

In conclusion, it seems appropriate to advise the specific group of women with an excellent prognosis of the evidence of this trial; those who prefer to avoid RT for reasons of psychology, geography, physical fitness or the desire to avoid side effects may choose tamoxifen alone. Since those falling into the Nottingham Prognostic Index Excellent Prognostic Group account for approximately 15% of all women with invasive breast cancer (particularly those diagnosed at breast cancer screening), hormonal therapy in place of RT following WLE for primary breast cancer could give a considerable saving in terms of machine usage and staff time[19]. Conversely, some women may prefer not to take tamoxifen as long-term medication, which is not without potential side effects (e.g. menopausal symptoms and thrombotic risks), and may prefer RT. Of note, it is well recognised that non-compliance with tamoxifen therapy may be an issue and we do not have information on how many women completed 5 years of tamoxifen therapy. However, some women will undoubtedly prefer to minimise the risk of LR and will select to

receive both treatments; it is clear from these data that those receiving both RT and tamoxifen have the lowest LR risk.

Intrinsic sub-types of invasive breast cancer have different outcomes and future management strategies would wish to exclude the more aggressive sub-types from minimal adjuvant therapy[20]. There have also been significant developments in both radiotherapy and endocrine therapy since the time of this trial, and these may be relevant in considering how the results of this trial inform treatment decisions today[21-23]. Given the very low recurrence rates achieved it is probable that any differences in local recurrence rates attributable to modern therapy would be too small to be readily-measured. No survival difference has been demonstrated between any of the treatment groups, so acceptability to individual patients takes on great significance. Aromatase inhibitors are now widely used instead of tamoxifen as the first choice adjuvant endocrine therapy for receptor-positive patients[21] and, although well tolerated by most patients, these drugs can cause significant side effects. Changes in radiotherapy have seen a move to shorter schedules, supported by randomised trials[22], and accelerated partial breast techniques. Current guidelines for use of partial breast radiotherapy suggest that it can now be offered to patients such as those treated in BASO II[23]. For most patients with excellent prognosis tumours, surgery alone offers too high a risk of local recurrence to be acceptable, but the decision as to whether to use endocrine therapy alone, radiotherapy alone, or both, will need to be tempered by full discussion of these options[24].

It should be noted that this is the situation at 10 years of follow-up. One problem, is a fall-off in follow-up information, exacerbated by cessation of follow-up by hospitals as routine. This is

particularly true in this group of women with excellent outcome as the risk of recurrence and metastasis is both low and very long-term. Use of actuarial analysis is designed to compensate for this, but assumes any bias arising from loss to follow-up applies to both sides in randomisation and that tamoxifen confers as good a long-lasting control as RT. The EBCTCG meta-analyses show little difference in late recurrence rates for either treatment at 10 years[18, 25] ENREF_21. In trials of the use of tamoxifen without other primary treatment, as an alternative to surgery in elderly patients[26-29], complete response was achieved in many cases and was maintained to at least 5 years in 85% of ER positive tumours. However, there remained a steady, small rate of recurrence after complete remission and tamoxifen was applied not only for five years (as in the present study) but until evidence of progression. Although figure 2 shows a steady rate of rise in LR to 10 years and no evidence that either treatment effect has worn off with time, longer follow-up is required from the present BASO II study.

Legends to Figures and Tables

Figure 1   Design and patient recruitment into BASO II trial

Figure 2   Survival to first local recurrence by treatment actually received

Table 1   All cases randomised. Local recurrences by RT and tamoxifen therapy according to randomisation by intention to treat. Absolute numbers of local recurrence at time of analysis, 10 year LR-free figures from survival analysis, hazard ratios and 95% confidence intervals.

Table 2   Local recurrence in the patients entered into the 4-way randomisation. Numbers of patients and local recurrence, rates of local recurrence, 10-year percentages local recurrence-free, hazard ratios and 95% confidence intervals
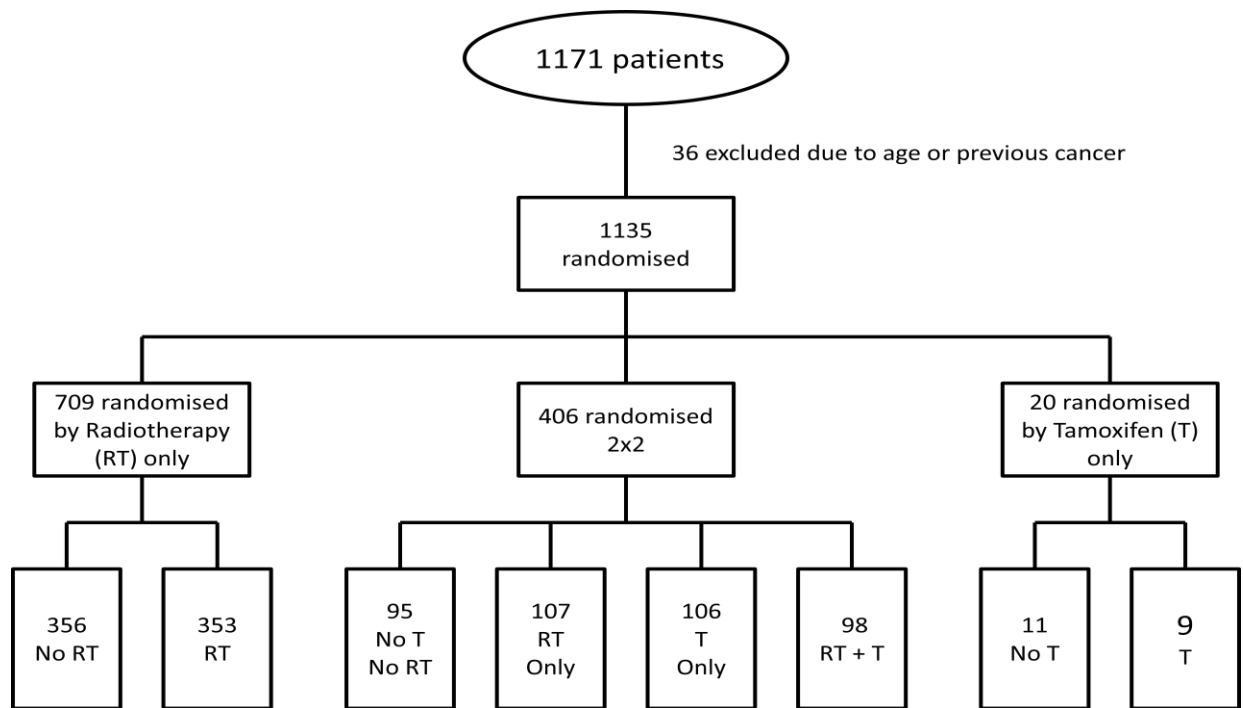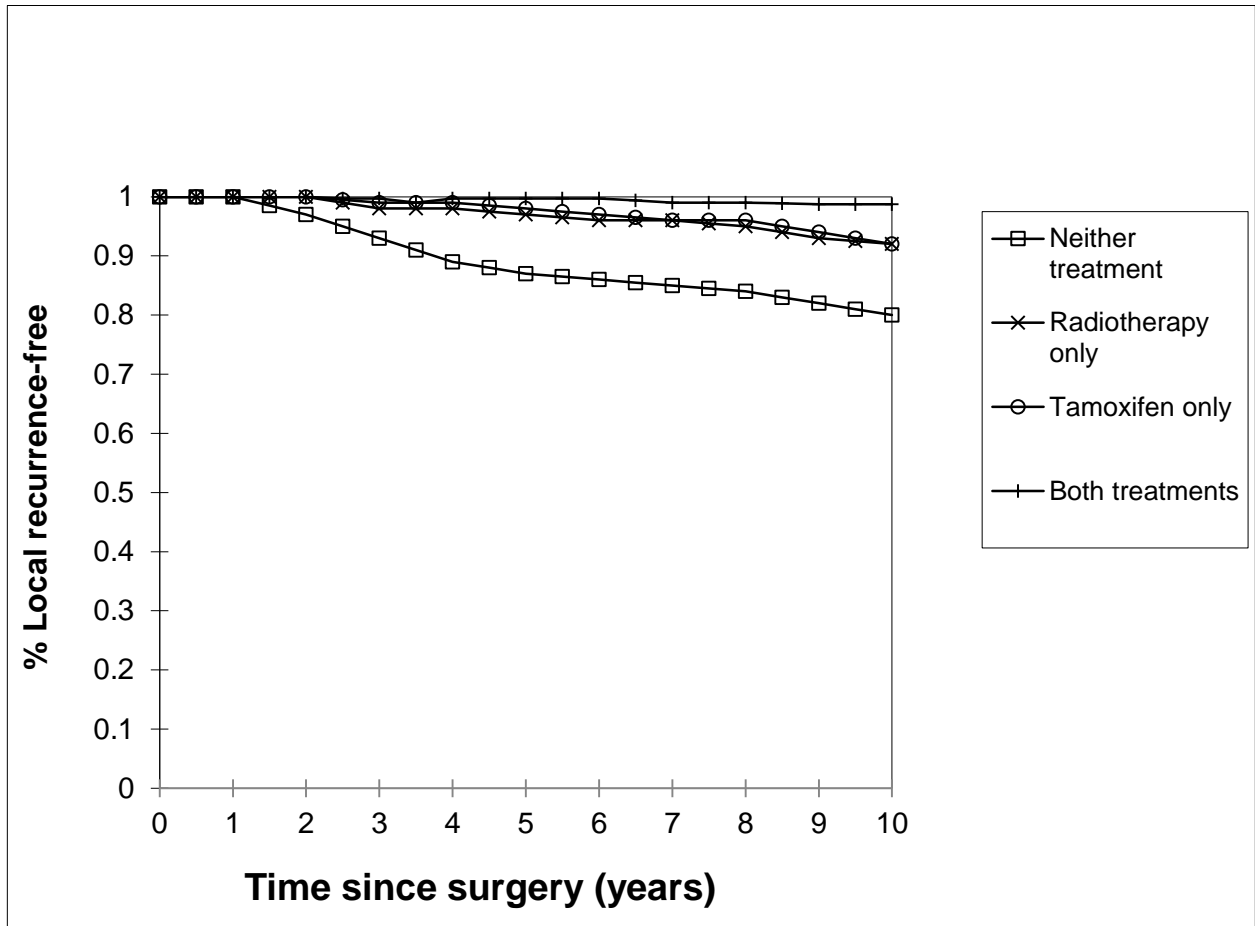
Figure 1. Patients randomised

Figure 2. Local Recurrence-free survival by treatment actually received

Quantity	Treatment randomised			
	No RT	RT	No tamoxifen	Tamoxifen
No. of patients	557	558	213	213
No. of LR	57	22	25	9
Annual % rate of LR	1.2	0.4	1.3	0.4
10-year % LR free	89	97	87	96
HR (95% CI)	1.00 (-)	0.37 (0.22-0.61)	1.00 (-)	0.33 (0.15-0.70)

Table 1. Local recurrence by RT and tamoxifen by intention to treat for all cases randomised. Absolute numbers of LR at time of analysis, 10-year LR-free figures from survival analysis, hazard ratios and 95% confidence intervals. LR, local recurrence; RT, radiotherapy; HR, hazard ratio; CI confidence interval

Quantity	Treatment randomised			
	Neither	RT only	Tamoxifen only	Both
No. of patients	95	107	106	98
No. of LR	15	7	8	0
Annual % rate of LR	1.9	0.7	0.8	0.0
10-year % LR-free	83	93	93	0
HR (95% CI)	1.00 (-)	0.37 (0.14-0.90)	0.40 (0.16-0.95)	0.00 (-)

Table 2. Local recurrence in the cases entered into the 4-way randomisation only. Numbers of patients and LR, rates of LR, 10-year percentages LR-free, hazard ratios and 95% confidence intervals. LR, local recurrence; PA, per annum

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