A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up

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Background: Long-term analysis of a randomised trial in Nottingham comparing tamoxifen versus surgery as initial treatment demonstrated that in oestrogen receptor (ER)-unselected cases, surgery achieved better local control, with

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no difference in overall survival. It was suggested that for patients with ER-rich tumours, local control and survival may be comparable. We now present long-term follow-up of a randomised trial designed to address this clinical scenario.

**Patients and methods:** One hundred and fifty three fit elderly (≥70 years) women with clinically node-negative primary invasive breast carcinoma ≤5 cm of high ER content [histochemical (H) score ≥100] were randomised 2:1 to primary tamoxifen (Tam) (N = 100) or mastectomy with adjuvant tamoxifen (Mx + Tam) (N = 53).

**Results:** With median follow-up of 78 months, there was no statistically significant difference in 10-year rates of regional recurrence (9.0% versus 7.5%), metastasis (8.0% versus 13.2%), breast cancer-specific survival (89.0% versus 86.8%) or overall survival (64.0% versus 86.0%) between Tam and Mx + Tam; however, local control was inferior with Tam (local failure rates 43.0% versus 1.9%; P < 0.001).

**Conclusion:** Irrespective of the degree of ER positivity, surgery achieved better local control. However, there was excellent and similar survival in both groups. Tam could be considered in those who are ‘frail’, refuse or prefer not to initially undergo surgery.

**Key words:** breast cancer, elderly, mastectomy, oestrogen receptor, primary tamoxifen

**Introduction**

The treatment of breast cancer in the elderly remains a controversial topic. Many centres adopt a policy of less aggressive management on the premise of perceived patient frailty whilst others consider that as the biological behaviour of the disease in this age group is no different to that in the younger population, then treatment protocols should be similar (for review, see Ashkanani et al. [1]). Tamoxifen was introduced as primary therapy for the elderly in the early 1980s following the encouraging findings of initial pilot studies [2, 3]. Whilst tamoxifen remains the treatment of choice for frail elderly patients with oestrogen receptor (ER)-positive tumours who are unable to tolerate surgical intervention, its empirical use in the fit elderly has more latterly been questioned as the majority of cases will eventually progress and require further treatment [4, 5].

At Nottingham, the issues of management in the fit elderly population have been addressed by two prospective randomised trials. In the first trial [elderly primary series (EPS) I], initiated in 1982, 131 cases were randomised to receive wedge mastectomy (N = 65) or primary tamoxifen (N = 66) as sole initial therapy, irrespective of ER status (ER was not routinely measured on the unit at this time) [6]. The final results of the trial after over 20 years have recently been reported [7] and have confirmed earlier findings [8] that whilst the rates of overall survival and metastasis were no different between the two treatment arms, local control was significantly inferior with tamoxifen compared with mastectomy. Even so, a significant subset of the elderly patients did go on to achieve a long-term response on primary tamoxifen. In order to define these latter patients more precisely, a second Nottingham trial (EPSII) was initiated in 1989 based on tumour ER content. One hundred and fifty three patients with breast cancers of histochemical (H) score based on ER immunohistochemistry ≥100 (out of 300) were randomised to receive primary tamoxifen (N = 100) or mastectomy + adjuvant tamoxifen (N = 53). EPSII remains unique to this day in that it has been the only trial to compare the outcome of these two treatment modalities specifically in tumours of high ER positivity. Early results on the initial endocrine response from the study were published in 1992 [9] and showed that by excluding cases with low ER content, the initial progression rate on primary tamoxifen was reduced from 26% (EPSI) to 3% (EPSII). The current paper reports on the long-term outcome of EPSII two decades following trial commencement [with median follow-up of 78 months (range 7–241)].

**Patients and methods**

Patients for EPSII were recruited from 1989 to 1996. Entry criteria were that each patient was ≥70 years old with T1/2, N0/1, M0 breast cancer and fit to undergo surgery with the adjunct that their breast tumour was of high ER positivity (ER H score ≥100). All the patients had given informed consent to enter the trial. ER expression was obtained from immunohistochemical assessment of pre-treatment fine needle aspiration cytology or needle core biopsy using the Abbott H222 antibody kit (Abbott, Chicago, IL). The methodology for the assay has been described previously [10]. The expression of ER was assessed using the semi-quantitative H score method (range 0–300) which takes into account both the percentage and the intensity of cellular staining, i.e. H score = (% cells with no staining × 0) + (% cells staining weakly × 1) + (% cells staining moderately × 2) + (% cells staining strongly × 3). A total of 102 patients were randomised to receive 20 mg primary tamoxifen daily (Tam) (two patients in the Tam group were subsequently excluded because of breach of randomisation protocol) and 53 to undergo simple mastectomy followed by 20 mg adjuvant tamoxifen daily (Mx + Tam) continued for up to 5 years. Randomisation was 2:1 in favour of tamoxifen in order to pick up the events in this group. The mean age of the patients (Tam = 78 years; Mx + Tam = 76 years; P = 0.07), level of ER expression (Tam H score = 169; Mx + Tam H score = 171; P = 0.86) and tumour size (Tam = 3.1 cm; Mx + Tam = 2.8 cm; P = 0.09) were similar in both treatment groups. In the surgical arm, lymph nodes were not routinely excised unless palpable, N = 7 (13%). In the tamoxifen arm, 14 (14%) cases had clinically palpable lymph nodes at presentation.

The patients were reviewed regularly in a dedicated Primary Breast Clinic for Older Women. In the Tam arm, clinical response was assessed by bi-dimensional calliper measurement of tumour size and categorised into complete response (CR—no palpable tumour remaining); partial response (PR—reduction of ≥50%); static disease (SD—reduction of <50%–25% increase) or progressive disease (PD—increase of >25% or appearance of new lesions in cross-sectional area according to International Union Against Cancer (UICC) criteria; 11). De novo progressors were classified as those with PD before 6 months on tamoxifen. Second-line therapy was decided on an individual patient basis at the time of relapse, treatment for locoregional recurrence/progression comprising mastectomy (for the Tam arm), axillary surgery, radiotherapy or second-line hormone therapy. Metastases were treated with further endocrine agents. Primary
outcome measures included comparison of rates of local and regional failure, metastasis, breast cancer-specific and overall survival between the two treatment arms; secondary measures were time to locoregional failure (PD by UICC criteria or regional progression for Tam group; local or regional recurrence for Mx + Tam group) and duration of response (D of R) on primary tamoxifen.

**statistical analysis**

All statistical analyses were performed using the SPSS data analysis program, Version 18 (SPSS UK Ltd.). Rates of local and regional failure, metastases, breast cancer-specific and overall survival at 5 and 10 years follow-up were compared using Pearson chi-square test. Actuarial survival and locoregional failure rates and D of R to tamoxifen were compared with life-table analysis using Gehan’s modification of the generalised Wilcoxon test.

**results**

**survival outcomes**

With a median follow-up of 78 months, we found there to be no statistically significant difference in the rates of regional recurrence, metastasis, breast cancer-specific survival or overall survival between the two treatment groups (Table 1). A non-significant early divergence of the survival curves for deaths from all causes was apparent (Figure 1) ($P = 0.21$ at 5 years), but at 10 years of follow-up, there was no difference in overall survival ($P = 0.80$).

**local control**

Whilst there were no significant differences in breast cancer-specific or overall survival detected in this series at 10 years of follow-up, locoregional control was found to be markedly inferior on Tam (Figure 2), with a local failure rate of 43% at 10 years compared with 2% for the Mx + Tam arm ($P < 0.001$). Forty-two percent of the Tam patients have required a second treatment, 15% a third and 7% a fourth for control of disease progression overall (including metastasis) compared with 13%, 0% and 0% in the Mx + Tam cases, respectively. Twenty percent of the Tam patients have undergone mastectomy, 36% have received further endocrine therapy and 6% have had radiotherapy; 9% percent of the Mx + Tam patients have received second-line endocrine therapy and 4% have undergone axillary clearance as subsequent treatments. There was only one case of uncontrolled locoregional disease in the series. This occurred in one of the Tam patients who refused to undergo surgery at the time of local progression (after 15 months on therapy). Another patient developed a new primary breast cancer (ER negative) after 38 months on tamoxifen. One patient in the Mx + Tam arm developed stage IV endometrial carcinoma and had tamoxifen changed to megestrol acetate. There were no cases of contralateral breast cancer in either treatment group.

**endocrine response**

The 6-month UICC clinical responses in the Tam cases are summarised in Table 2; 46% of cases eventually achieved CR.

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**Table 1. Actuarial rates of recurrence, metastasis and survival by treatment groups—EPSII**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Follow-up (years)</th>
<th>Primary tamoxifen (%)</th>
<th>Mastectomy + adjuvant tamoxifen (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local failure</td>
<td>5</td>
<td>38.0</td>
<td>1.9</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>43.0</td>
<td>1.9</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Regional failure</td>
<td>5</td>
<td>8.0</td>
<td>5.7</td>
<td>0.594</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9.0</td>
<td>7.5</td>
<td>0.759</td>
</tr>
<tr>
<td>Metastasis</td>
<td>5</td>
<td>8.0</td>
<td>7.4</td>
<td>0.762</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8.0</td>
<td>13.2</td>
<td>0.303</td>
</tr>
<tr>
<td>BCSS</td>
<td>5</td>
<td>92.0</td>
<td>92.5</td>
<td>0.921</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>89.0</td>
<td>86.8</td>
<td>0.687</td>
</tr>
<tr>
<td>OS</td>
<td>5</td>
<td>74.0</td>
<td>83.0</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>64.0</td>
<td>66.0</td>
<td>0.802</td>
</tr>
</tbody>
</table>

BCSS, breast cancer-specific survival; OS, overall survival.
However, 14 of these have since progressed (time to progression range 19–108 months). The longest continued CR has been for 108 months. A total of 43% of the Tam patients remain in response at the present follow-up; 14 of the continued responders having died of unrelated causes without requiring further treatment of their breast cancer. D of R was assessed according to the best response achieved on tamoxifen. The CRs achieved significantly the longest D of R of all the response groups (Figure 3); yet, whilst the PRs and SDs had a shorter D of R than those women with CR, this did not appear to compromise overall survival, there being no significant difference in breast cancer-specific survival or deaths from all cause between any of the four response categories (full data not shown).

discussion

Over the past few decades, primary tamoxifen has gained much popularity in the treatment of elderly women, often being considered as the ‘easy option’ by patient and physician alike. Primary endocrine therapy (e.g. using tamoxifen or more latterly aromatase inhibitors) remains the treatment of choice for frail elderly patients unable to tolerate surgical intervention for ER-positive primary breast cancer. The long-term results from several studies, including the present, have reported that surgery followed by adjuvant tamoxifen appeared to confer a greater benefit than tamoxifen alone in the fit elderly population [12–14]. While it does not reach statistical significance, the trend in the current study in favour of surgery plus adjuvant tamoxifen suggests that this is the case even in tumours of high ER positivity (with H score ≥100).

Nevertheless, selection according to ER does play an important part in the clinical outcome of patients treated by primary endocrine therapy. Compared with the EPSI, selection for high ER expression has resulted in a greater initial response rate (from 59% to 75% objective response at 6 months; Table 3), a reduced proportion of de novo progressors (from 26% to 3%; Table 3) and an improved local control rate (local failure rates at 10 years decreased from 80% to 43%) [7–9]. The rate of uncontrolled locoregional failure in the Tam arm was negligible and the majority of patients (80%) did not require mastectomy. This is in line with our recently published study evaluating the long-term clinical outcome of ER-positive invasive primary breast carcinoma in 1065 older women [15]. Among the 616 patients who received primary endocrine therapy, all patients having tumours with an ER H score of ≥250 had clinical benefit at 6 months. These patients had a significantly better breast cancer-specific survival compared with those who progressed before 6 months, and they also had similar breast cancer-specific survival compared with those patients treated with initial surgery. Thus, a higher H score (such as 250) may be required, when using primary endocrine therapy, to achieve an outcome comparable to initial surgery.

Figure 2. Actuarial locoregional failure (disease progression) rates by initial treatment (Mx + Tam N = 53; Tam N = 100; P < 0.001).

Figure 3. Duration of response on primary tamoxifen by best response (International Union Against Cancer criteria) [complete response (CR) N = 46; partial response (PR) N = 35; static disease (SD) N = 16; pairwise analyses: CR versus PR P = 0.005; CR versus SD P < 0.001; PR versus SD P = 0.003].

Table 2. Endocrine response on primary tamoxifen—EPSII

<table>
<thead>
<tr>
<th>UICC response status</th>
<th>6-Month response (%)</th>
<th>Best response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>PR</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>SD</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

CR, complete response; EPS, elderly primary series; PR, partial response; SD, static disease; PD, progressive disease; UICC, International Union Against Cancer.
Table 3. Endocrine response at 6 months on tamoxifen—EPSI versus EPSII

<table>
<thead>
<tr>
<th>6/12 Response status</th>
<th>EPSI (ER unselected) (%)</th>
<th>EPSII (high ER content) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>59</td>
<td>75</td>
</tr>
<tr>
<td>SD</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>PD</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>

EPS, elderly primary series; ER, oestrogen receptor; OR, objective response; SD, static disease; PD, progressive disease.

Whilst the difference in local control is clear from the study, we did not identify a statistically significant advantage in survival with upfront surgery. Although there was a non-significant divergence of the overall survival curves at 5 years, with continued follow-up and as this present final analysis shows, the divergence disappeared at 10 years and statistical analysis has shown no difference in overall survival between the two treatment arms. This is consistent with the results of a meta-analysis of 1571 older patients with primary breast cancer recruited in seven randomised trials (including EPSI and II) showing no difference in overall survival between surgery and primary endocrine therapy [16].

Irrespective of the degree of ER positivity, primary tamoxifen led to progression in a large proportion of cases. Thus, surgery remains the treatment offering the lowest chance of local failure. However, there was excellent and similar breast cancer-specific and overall survival in both treatment groups, even at 10 years. Of further note is that between 5 and 10 years follow-up, the incidence of metastases, regional failure and even local progression are low. For local progression, the rate rose from 38% after 5 years follow-up to 43% after 10 years. It would therefore seem that there is a large subgroup of patients who have strongly ER-positive tumours (approximately half of the type of patients in this study) which can be controlled long term and that if the tumour is still controlled after 5 years on tamoxifen it is highly likely to remain controlled by 10 years of follow-up. Identifying such a subgroup of patients at diagnosis remains a challenge.

Primary tamoxifen can be considered in those who are ‘frail’ (with limited life expectancy), refuse or prefer not to undergo initial surgery. Using a more stringent selection method according to tumour biology (e.g. a higher ER H score and perhaps a further biological factor) as well as using an aromatase inhibitor instead of tamoxifen may further improve the clinical outcome for primary endocrine therapy in this population.

disclosure

The authors declare no conflict of interest.

references