

## Invited review

## Breast cancer in the elderly

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*As the expectation of life in the Western world increases the incidence of breast cancer rises and more and more of our patients present over the age of 70. The expectation of life amongst women in the UK is now 85 so a fit “elderly” woman of 70 has many years left for the natural history of breast cancer to express itself. Never the less the older the woman with breast cancer the more likely she is to die of co-morbidity. The first point to make therefore is that age alone should not be a determinant of therapy but that should remain a decision based on the stage and biological variables within the primary tumour. In spite of all that there may be a place to compromise on default therapies if the expectation of life of the woman is say less than three years. I will illustrate these points by focussing on three trials with which I’ve been actively involved.*

*The first are the trials comparing surgery plus tamoxifen versus surgery alone in women over the age of 70, secondly the TRAGIT trial of intra-operative radiotherapy and thirdly the ATAC trial comparing tamoxifen with arimidex. I will argue that surgery is still required in primary therapy in the elderly whose expectation of life exceeds 3 years but also there is room for a new trial of aromatase inhibitors as sole therapy for women with tumours that express the ER and are say 80 years or more at presentation. I also believe that there is a place for IORT for women with serious co-morbidity and I will argue that there may be an age of transition when tamoxifen might be favoured above aromatase inhibitors as first line adjuvant therapy.*

**Key words:** breast cancer, elderly

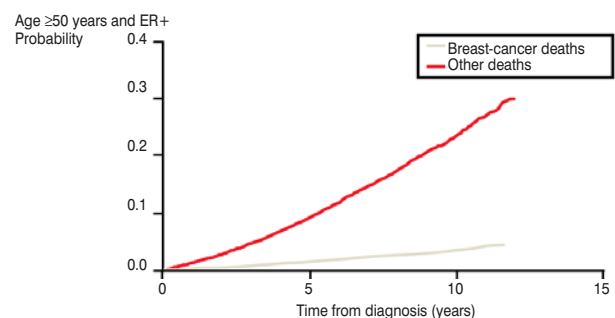
## Introduction

As the expectation of life in the Western world increases the incidence of breast cancer rises and more and more of our patients present over the age of 70. The fact that I have passed my 70<sup>th</sup> birthday and yet still feel a spring in my step, illustrates the point that as well as living longer many of us live healthier lives as well. The expectation of life amongst women in the UK is now 85 so a fit “elderly” woman of 70 has many years left for the natural history of breast cancer to express itself. Furthermore because of the “survival of the fittest” it is estimated that a woman aged 80 has an expectation of life of 89 and a woman of 86 can still expect to survive another 6 years if free of serious co-morbidity. Against that, on average, overall survival of women >80 with breast cancer is 72% at 1 year and 58% at 5 years [1]. Never the less the older the woman with breast cancer the more likely she is to die of co-morbidity (see Figure 1).

The first point to make therefore, is that age alone should not be a determinant of therapy but that should remain a decision based on the stage and biological variables within the primary tumour and the presence or absence of co-morbidities. Furthermore there is no truth in the belief that elderly women value their breasts less than younger women.

In spite of all that there may be a place to compromise on default therapies if the expectation of life of the woman is say less than three years. I will illustrate these points by focussing on three trials with which I’ve been actively involved.

The first is the CRC trial comparing surgery plus tamoxifen versus surgery alone in women over the age of 70 [2], the second is the TARGIT trial of intra-operative radiotherapy [3] and the third is the ATAC trial comparing tamoxifen with arimidex [4]. I will argue that surgery is still required in primary therapy in the elderly whose expectation of life exceeds 3 years but also there is room for a new trial of aromatase inhibitors as sole therapy for women with tumours that express the ER and are say 80 years or more at presentation. I will also argue, that one shot of intra-operative radiotherapy



ER+, oestrogen receptor-positive

Hanrahan et al. J Clin Oncol 2007; 25: 4952-60

**Figure 1.** Competing causes of mortality

after breast conserving surgery might suffice and finally that there may be an age of transition when tamoxifen might be favoured above aromatase inhibitors as first line adjuvant therapy.

### **Trials of tamoxifen alone versus surgery plus tamoxifen**

Following the early successes of tamoxifen in the advanced and adjuvant setting reported in the early 1980s [5] it became fashionable to treat breast cancer in the “elderly” off protocol with tamoxifen alone. To try and make sense of this before “fashion” became standard practice, my group launched a trial of tamoxifen alone versus surgery plus tamoxifen for women over the age of 70 [2].

The two major end points were progression free survival (PFS) and overall survival (OS). The results are illustrated in Figures 2 and 3. It is clear that in just under two years 50% on tamoxifen alone were judged to be treatment failures and most of them went on to have delayed surgery when presumably they were older and less fit. Yet the intriguing results for OS demonstrates that for three years the lines are superimposed. Incidentally as far as I can recall this was the first trial ever to show that surgery had an impact on survival.

So far there have been three trials of a similar design that have been systematically reviewed, with the conclusion that tamoxifen alone for the “elderly” is not adequate treatment [6]. Why does this approach fail? Firstly as already stated the life expectancy of a woman of 70 is 13 years or more if otherwise healthy and clearly tamoxifen alone cannot control the disease for that long as the tumours by be de novo resistant or acquire resistance over time. Secondly only one of the three trials used ER status to select patients and even if the large majority of tumours in women in this age group are ER+ clearly the trials were flawed. However, the survival curves in the CRC trial did not diverge for the first 3 years despite having an unselected population so perhaps we should revisit the issue. We now have increasing number of older patients who are living longer with several co-morbidities. Furthermore we have a new

class of compound, the aromatase inhibitors (AI) that are better than tamoxifen and are just as easy to use. For example in the IMPACT trial, the overall response rate for anastrozole was significantly better than tamoxifen when used as neo-adjuvant therapy [7].

I would therefore advocate designing a new trial for women older than say 80 with hormone responsive tumours comparing an AI alone with surgery plus an AI with the drug administered until relapse.

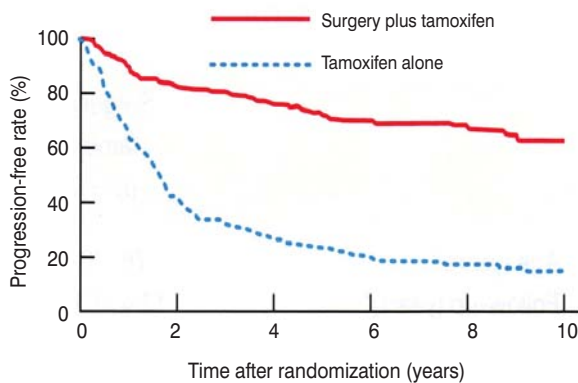
### **Can we avoid XRT after BCS in elderly?**

Postoperative radiotherapy is certainly an ordeal for elderly women. The physical demands of repeated journeys to and from the hospital for 6 weeks must be exhausting and often makes extra demands on their families and carers. Furthermore cardiac co-morbidity adds to the potential hazard of the treatment.

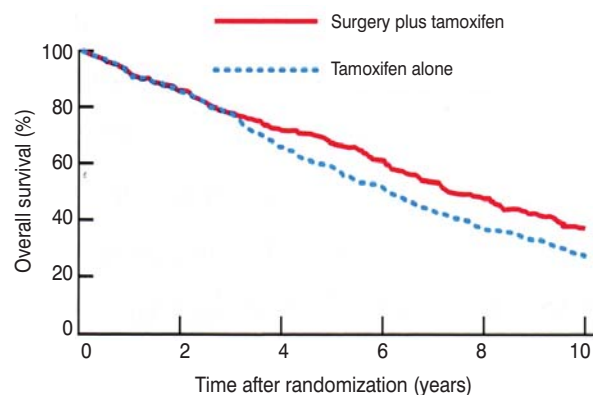
The EBCCTG and Milan trials both failed to show an effect in the reduction of local recurrences in the age group considered but that might have been because are the small sample size, co-morbidities or very low base line values [8, 9].

A number of trials are being set up at the moment to compare no radiotherapy versus conventional beam external beam treatment. (e.g. UKNCRN trial)

To my way of thinking one shot of intra-operative radiotherapy (IORT) might be the ideal compromise in this age group. My group has been investigating IORT using the “INTRABEAM” devise (Figure 4) for over 10 years [3]. The clinical rationale is based on the fact that in spite of the multi-focality of breast cancer in nearly 70% of cases as defined by the microscopic analysis of mastectomy specimens, 90% of local recurrences (LR) occur in the index quadrant. Since the adoption of adjuvant endocrine therapy, the chance of a LR occurring outside the index quadrant is about the same as the chance of a new contra-lateral breast cancer. If that is the case then it makes as much sense to treat the non -index quadrants of the ipsi-lateral breast as to treat contra-lateral breast. The TARGIT trial comparing whole breast irradiation (EBRT) versus IORT alone is close to completion [10] but in the meantime it is worth



**Figure 2**



**Figure 3**

**Figures 2, 3.** Trials of tamoxifen alone versus surgery plus tamoxifen for women over the age of 70 – comparison between progression-free survival (PFS) and overall survival (OS)



Figure 4. INTRABEAM

noting the results of a series of patients treated with IORT alone because they were unsuitable for EBRT because of age or serious co-morbidity [1]. The LR rate in this group has been negligible and the deaths so far have been from co-morbidity. A new trial, TARGIT E, comparing EBRT with IORT or no treatment in >70 years age group is currently being planned by Professor Joseph's group in Perth WA. Pending that it would be reasonable to treat elderly women who are unwilling to make the journeys to a from the radiotherapy centre, with IORT alone after BCS.

### Is there justification to select tamoxifen rather than an AI, as adjuvant endocrine therapy, based on age because of fracture risk and competing risks for mortality?

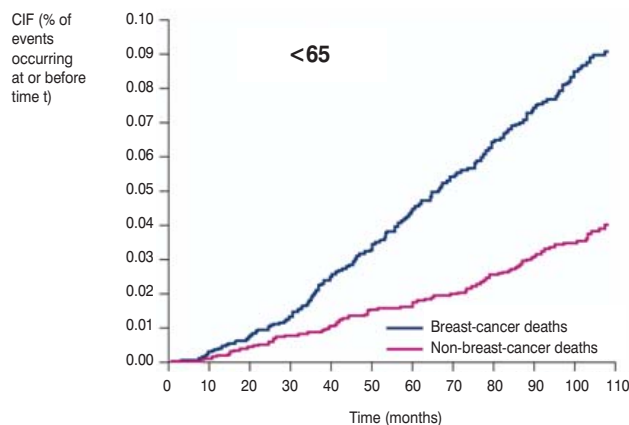
The ASCO (US) and NICE (UK) guidelines recommend the use of an aromatase inhibitor AI rather than tamoxifen, at some point in the management of all ER+ breast cancer patients who are postmenopausal at the time of diagnosis. This advice was heavily influenced

by the ATAC trial, the first to report on this subject during the time I was acting as principle investigator, in 2002 [4]. The latest results of this study were reported in *Lancet oncology* in 2007 [13]. The mean at the 100 months' median follow-up was 72 years. After treatment completion (5 years), fractures and serious adverse events continued to be collected. At a median follow-up of 100 months, statistically significant improvements were seen for anastrozole in the hormone receptor-positive subpopulation, the clinically important subgroup for which endocrine therapy is now known to be effective. Absolute differences in disease free survival increased over time, 2.8% (anastrozole 9.7% vs tamoxifen 12.5%) at 5 years and 4.8% (anastrozole 17.0% vs tamoxifen 21.8%) at 9 years and thus hazard rates remained lower on anastrozole after treatment completion. The reduction in deaths after recurrence was not statistically significant and no effect was seen for overall survival (OS) (HR=0.97, 95% CI 0.86-1.11, p=0.7). Fracture rates were higher with anastrozole than tamoxifen during treatment but not different after treatment was completed. There was no evidence of an increased risk of cardiovascular morbidity or mortality at 100 months' median follow-up. These data clearly established the long-term efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer and provided the first definitive evidence on the existence of a carryover benefit following 5 years adjuvant treatment with anastrozole.

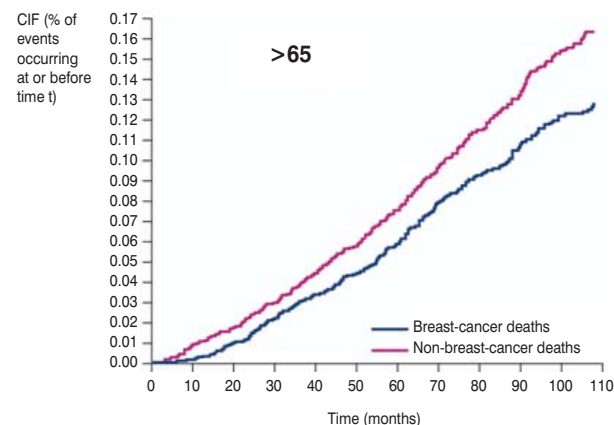
However there is a paradox to be explained in that there was a highly significant reduction in DFS favouring the AI, close to 5% in absolute terms, yet no significant difference in overall or cause specific mortality.

My personal explanation for this is related to the age of the patients in the study.

Figure 5 demonstrates the fact that significantly more women >65 in the ATAC trial die from co-morbidity rather the breast cancer and the reverse applies to women under the age of 65 [14]. Furthermore the



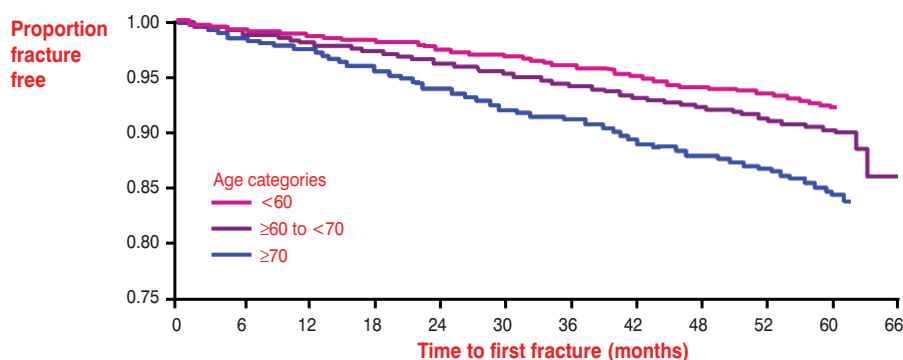
CIF, Cumulative Incidence Function



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Buzdar at al ASCO 2008

Figures 5. Effect of age on the number of deaths without recurrence and following recurrence (anastrozole and tamoxifen arms combined)



**Figure 6.** Kaplan Meier: probability of time to first fracture age  
Patients who have not had a fracture during trial therapy are censored after the number of days of trial treatment received

excess risk of a fracture in the AI treated group compared with tamoxifen increase with age. (see Figure 6). I believe this dilutes out the potential benefit of AIs to reduce breast cancer specific mortality and increase overall survival. Bearing in mind that tamoxifen is seen as an agonist for skeletal health, and that fractures in the elderly can lead to premature death from pneumonia or thrombo-embolic disease, then I suspect although purely speculation at the moment, that there may be a cross over point at say the age of 70, when T might be favoured over A. Longer term follow up of the ATAC trial will address that question but in the meantime I would favour T over A in elderly women with a low bone mineral density or established osteoporosis.

## Conclusions

“Elderly” is a somewhat subjective term. Ideally women should be treated for breast cancer according to their physiological rather than their chronological age. If that is the case I don’t think we should compromise on treatment just because a woman is aged >70. However if there is serious co-morbidity with an expectation of life of <3 years a trial of tamoxifen alone might be in order. For other women over the age of 80 trials with ER+ tumours trials of an AI alone are required. For women undergoing breast-conserving surgery over the age of 70, trials of EBRT versus IORT or no post operative radiotherapy are in the planning stages. In my opinion IORT off protocol is an option for women with serious co-morbidity. Finally I keep an open mind about the harm/benefits of tamoxifen versus an AI for women >70 although those with established osteoporosis should preferably be treated with tamoxifen.

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