

Review

Primary endocrine therapy as a treatment for older women with operable breast cancer – A comparison of randomised controlled trial and cohort study findings



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Abstract

Introduction: One third of all breast cancers occur in women over the age of 70. Primary endocrine therapy (PET) is used in some women to minimise morbidity in a population with higher rates of comorbidity and frailty. In the UK up to 40% of women over 70 are treated with PET although there is a high rate of variability of practice between centres reflecting a lack of guidance about case selection.

Methods: A systematic review of the literature was performed to try and establish if this form of treatment is still valid in modern breast practice.

Results: Six randomised controlled trials (RCTs) and 31 non-randomised studies were deemed eligible. Available data demonstrate an advantage for surgery over PET in terms of disease control and a likely survival benefit in patients with a predicted life expectancy of five years or more. Patients treated only with aromatase inhibitors (AIs) had superior rates of disease control when compared to Tamoxifen.

Conclusions: Guidelines to aid selection are needed but PET should be reserved for patients with reduced predicted life expectancy (e.g. less than five years), with AIs being preferable over Tamoxifen.

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Keywords: Breast cancer; Primary endocrine therapy; Surgery; Elderly; Systematic review

Background

Breast cancer incidence increases with age, with over 30% of breast carcinomas occurring in women aged 70 and older.^{1–3} This incidence is set to rise even further as the UK population ages.⁴

Elderly women are more likely to be diagnosed with oestrogen receptor (ER) positive breast cancers⁵ and therefore be responsive to anti-oestrogen therapy, hence the use of primary endocrine therapy (PET) in this age group. PET differs from neo-adjuvant endocrine therapy where an anti-oestrogen is used to down-stage a tumour prior to surgical treatment, usually to facilitate breast conserving surgery. Tamoxifen as PET was introduced and proved effective

for the treatment of breast cancer in the 1980s,⁶ after which it rapidly gained popularity in the UK as a management strategy for older women. This led to a number of randomised controlled trials (RCTs) aimed at comparing the efficacy of PET against surgery in older patients. In total 7 RCTs were performed internationally, all assessing Tamoxifen, although a variety of designs and comparisons were used. A Cochrane meta-analysis demonstrated superior local control with surgery but no increased survival benefit. As a result of this, more recent studies have advocated the use of PET only for the very frail or very old.^{7,8} This has a huge impact of the applicability of the RCT data to modern day clinical practice as all the included patients, by their very nature, were deemed fit enough for surgical treatment. In addition, since this data was published, Tamoxifen has largely been replaced by the third generation aromatase inhibitors as first line treatment for both PET and adjuvant therapy, again limiting the applicability of these earlier

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RCT results. Additionally, since the first studies on PET were published, other significant advances have been made in terms of the widespread availability of ER testing and improvements in anaesthetic techniques meaning that breast surgery today, even in the older patient, has a very low morbidity and mortality. This can be seen in the recent UK wide National Mastectomy and Reconstruction Audit, where the overall mortality rate was 0.26%.⁹ However this may reflect the fact that the less fit, frailer patients were managed with PET as this remains a widespread option for those considered at higher risk of surgery with 93% of UK surgeons using this option for some patients.¹⁰ Several recent studies have found that up to 40% of patients over 70 years old are treated with PET in the UK.^{11,12} Additionally, there have been several new studies published within the last two years looking at cohorts of women treated using PET.^{13–22} The methodology of these cohort studies vary greatly, particularly in terms of the treatment used, the fitness of included patients and whether ER testing was performed, again limiting the overall applicability to modern clinical practice. With such changes occurring in this field and with new data being published so recently, we undertook an analysis of the data pertaining to PET that has been published in the literature since it was introduced as a treatment for operable breast cancer.

Methods

A comprehensive search of the published literature was performed to identify studies that assess primary endocrine therapy in a clinical setting, by searching MEDLINE, EMBASE, CINAHL and PsychINFO databases. Searches were limited to those published after 1980 and published in the English language. References of all retrieved and relevant publications identified by the search strategies were searched for further studies.

A total of 6629 results were generated by these initial searches. Abstracts and titles were reviewed for relevance and compared to the inclusion criteria and full text articles were obtained. Where it was unclear from the title/abstract whether the studies met the inclusion criteria, full text articles were also obtained and a decision made based on the entire paper. See Fig. 1 for the review process.

Articles were deemed to meet the inclusion criteria if: they reported on older women (average age ≥ 70 years) with potentially operable primary breast cancer (i.e. stages I–IIIa) treated with PET. Exclusion criteria included studies where patients with stage IIIb or IV disease made up more than 30% of the population and those who were treated with neo-adjuvant endocrine therapy prior to surgery for a period of less than 6 months.

Data was extracted pertaining to number of patients, type of anti-oestrogen used, ER status, complete response rate (CR), partial response rate (PR), static disease (SD), progressive disease (PD), clinical benefit rate (CR + PR + SD), disease progression, breast cancer-

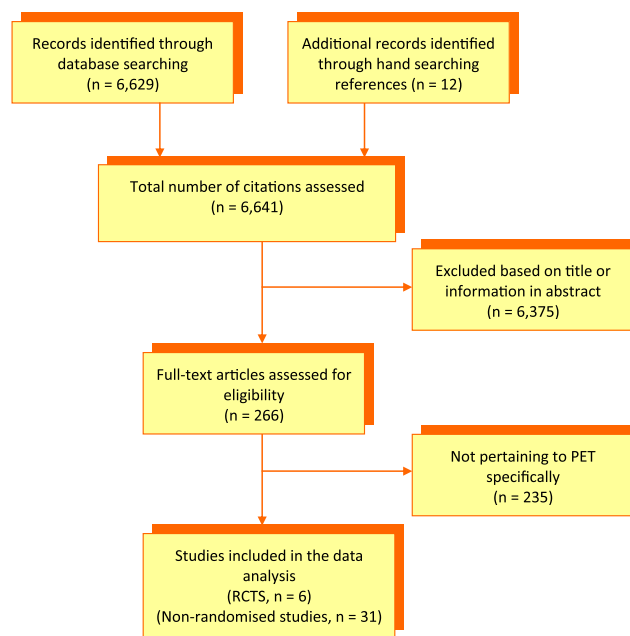


Figure 1. PRISMA diagram showing the review process.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi: [10.1371/journal.pmed.1000097](https://doi.org/10.1371/journal.pmed.1000097). For more information, visit www.prisma-statement.org

specific survival (BCSS) and overall survival (OS). Data analysis was performed using SPSS[®] software version 20 (IBM[®]). Associations were identified using Chi² analysis.

Results

Results of the search

Six randomised controlled trials (see Table 1) and 31 non-randomised studies (see Tables 2a and 2b) were deemed eligible for inclusion in the final review. In addition, two large population-based studies which analysed registry data for older patients with breast cancer were also identified. The randomised controlled trials identified were the same as those published in a Cochrane review^{23–25} and so these studies were not re-analysed but a brief overview will be presented here.

Efficacy of PET

A total of 31 cohort studies assessed a total of 2874 patients who were treated with PET. Of these, only 12 studies included solely patients who had ER positive tumours, 12 studies included patients with ER positive and ER negative tumours and 7 studies didn't assess ER status. Therefore the total number of patients in the studies including only ER positive tumours was 1417 and the number of patients in the studies including both ER positive and ER negative

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