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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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Authors: J.L. Morgan[a]*, M.W. Reed[a] and L. Wyld[a]

*corresponding author.

Authors' Affiliation Address: [a]Department of Surgical Oncology, E Floor, Medical School, Royal Hallamshire Hospital, University of Sheffield, Glossop Road, Sheffield, S10 2JF, UK.

E-mails: j.morgan@sheffield.ac.uk, m.w.reed@sheffield.ac.uk, l.wyld@sheffield.ac.uk

Tel: +44 (0)114 271 3611

Fax: +44 (0)114 271 3314

Abstract:

One third of all breast cancers occur in women over the age of 70. Breast cancer specific outcomes in this age group are inferior to those of younger women due to a combination of later stage at diagnosis and reduced treatment schedules. The latter are selected to minimise morbidity in a population with higher rates of comorbidity and frailty. One such treatment strategy is primary endocrine therapy (PET), where for women with potentially operable, oestrogen receptor positive (ER+) cancers surgery may be omitted in favour of anti-oestrogens alone. Twenty years ago, several randomised trials demonstrated that PET, whilst associated with lower rates of local disease control compared to surgery, offered equivalent overall survival rates. These trials were all flawed in not testing the ER receptor status of the cancer and not selecting a cohort of frailer women as would happen in current clinical practice. The data from these trials may therefore not be valid in modern practice.

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. It is likely that in frailer women with confirmed ER positive cancers, PET may be an effective alternative to surgery This systematic review of the literature relating to PET has included not only the RCT data but also cohort study data of actual clinical practice to try to establish if this form of treatment is still valid in modern breast practice

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 cancers [5] and therefore be responsive to anti-oestrogen therapy, hence the use of primary endocrine therapy (PET) in this age group. 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 lead 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 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, CINHAL 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 6,629 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 Figure 1 for the review process.

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-specific survival (BCSS) and overall survival (OS). Data analysis was performed using SPSS® software version 20 (IBM®). Associations were identified using Chi^2 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 patients was 1348. In general, the studies where ER was not known were less recent than those where ER status was known reflecting the increased availability of routine testing.

Nineteen studies including 1256 patients used TAM only; five studies including 325 patients used AIs only (Letrozole in three, Anastrazole in one and one did not specify); six studies including 1134 patients used both TAM and AIs; and one study that included 50 patients didn't specify the type of PET used.

Most studies included only elderly patients, with the average patient age being over 70 years. Follow-up length varied greatly, with the largest study having a follow-up range of between 1-202 months.

Not all studies reported on all outcomes, however there were enough studies to meta-analyse data on clinical benefit and progression rate according to PET type[¥] and ER status. Clinical benefit (CR+PR+SD) was higher in patients treated with an AI compared to patients treated with TAM (88% v 77%; $p<0.01$) and the rate of disease progression was lower in patients treated with AIs compared to TAM (31% vs. 46%; $p<0.01$).

We also analysed studies according to whether they included only ER positive patients or not. Studies who only included ER positive patients has a higher clinical benefit rate (86% v 75% $p<0.01$), although the rate of disease progression was the same between groups (41% v 41%).

Due to the large variation in follow-up length, it was not possible to analyse data on Breast Cancer Specific Survival or Overall Survival according to type of PET used or ER status.

Surgery vs. PET.

Six of the non-randomised studies, including 3559 patients, compared PET with surgery* – see tables 2a and 2b. Combining the results of the five studies that reported on OS revealed that there was a significantly higher overall

survival rate in patients treated with surgery when compared to those treated with PET (67% v 49% p<0.01). This is to be expected because of the likely difference in comorbidity, frailty and age between the PET and the surgery groups in a cohort study. Looking at BCSS, five studies reported on this outcome and meta-analysis demonstrated that surgery was associated with a small but significantly higher BCSS rate when compared to PET (90% v 85% p<0.01). The difference in effect size of the 2 treatments between surgery and PET arms comparing OS and BCSS is to be expected, again due to differing levels of comorbidity between the 2 groups. To date, there have also been seven Randomised Controlled Trials (RCTs) that have compared survival outcomes of primary Tamoxifen with surgery (with or without Tamoxifen) for the treatment of operable breast cancer in older women. Based on 869 deaths in 1671 women, meta- analysis was unable to demonstrate any significant difference between the two treatments in terms of overall survival when baseline patient characteristics are matched as in a RCT. However, PET was associated with a lower disease-free survival when compared to surgery due to a significantly increased rate of local disease progression in the breast in the PET arm of these trials.

In addition, two large population-based cohort studies also compared outcomes in patients according to the type of treatment they received. These studies were not included in the above meta-analysis as they did not specifically assess the use of PET as a treatment for older women, instead they looked at differences in outcomes for patients treated with surgery vs. non-surgical treatment. Additionally, both studies obtained their results from cancer registries which leads to concerns regarding data quality; as such they were considered methodologically too different to include in the meta-analysis. Bouchardy et al [56] reviewed the outcomes of 407 breast cancer patients aged 80 years or over, treated between 1989 and 1999. They found that 5-year specific survival was low among women who were treated with Tamoxifen only (51%) when compared to those women treated with breast-conserving surgery and adjuvant treatment (90%) [56]. More recently, Ali et al [57] reviewed the outcomes of 14 048 women with breast cancer, who were aged 50 years or older and treated in the East of England between 1999 and 2007. They also found that surgery was associated with superior overall survival relative to non-surgically treated women but selection bias for older, frailer women may have accounted for much of this difference and could not be corrected for due to innate limitations in registry data [57].

Discussion

When looking at the efficacy of PET, clinical benefit rates in elderly women with ER positive breast cancers are generally high and overall the cancer reduces in size or fails to progress in 75% of cases [23,24]. However, most of the original published RCTs recruited patients regardless of their ER status. Patients with moderate to strongly ER positive breast cancer can expect a good response in around 79-90%, this is in comparison to up to a 100% progression rate in patients with ER negative tumours [32,47,52,58-59]. This can be seen from the non-randomised data where there is a significantly higher response rate for those trials that included only ER positive patients.

Efficacy of PET also appears higher for patients treated with aromatase inhibitors rather that Tamoxifen, which is consistent with the findings from studies in other settings for this population, including the adjuvant, neo-adjuvant and metastatic settings, where aromatase inhibitors are well-established as the superior option [60-64].

In terms of survival benefit, there is no clear advantage to either treatment shown by the meta-analysis of the RCTs published to date. However, many of these trials were flawed by modern standards, particularly with regards the treatment given; three out of the seven trials used a comparison of surgery *only* – when nowadays, all patients undergoing operative intervention would be treated with adjuvant endocrine therapy where appropriate. This is without taking into account modern surgical techniques, with adequate margins and the routine addition of radiotherapy to patients who undergo wide-local excision.

Looking at the non-randomised studies, the combined data showed an advantage in terms of both overall and breast-cancer specific survival in favour of surgery. However, it must be noted that due to the selection criteria for these two groups of patients, particularly in terms of fitness for surgery and co-morbidities, the overall health status of the two populations are likely to be inherently different which will result in confounding when looking at OS as it includes all-cause mortality, something that would be expected to be higher in a less fit cohort. Breast cancer specific survival should be less subject to bias associated with baseline fitness levels between groups than overall survival and as this also favours surgery, this is of potential clinical significance. It suggests that in studies of what may be regarded as 'normal clinical practice' (as opposed to the artificial conditions imposed by RCTs) there is still some advantage to surgery except in women with a very high burden of comorbidity or frailty who die of non-breast cancer related diseases within a few years of diagnosis. However there is another potential source of bias to consider: that of death certification. If a woman has had surgery and has no evidence of local recurrence and dies of unrelated illness, breast cancer may not be mentioned on the death certificate. If she is on PET and still has a palpable or visible breast cancer, she may be more likely to have the breast cancer listed as a contributing cause, even when this was not the case. This phenomenon is increasingly recognised as a potential bias in observational studies using death certification to assess cause of death [65].

The co-morbid status and ages of the patients varied greatly between randomised and non-randomised studies. Co-morbidities have been demonstrated to have a significant impact on survival, and even those elderly women who are fit for surgery die of co-morbid diseases, thereby potentially reducing the survival advantage of any breast cancer therapies [66]. Mansi and colleagues [39] included a 29 year old patient in their study which, in terms of modern day practice, would be considered a wholly inappropriate indication for PET. The majority of studies took 70 years as a cut off for "elderly" and most did not comment on the level or type of co-morbidities, instead just quoting that included patients were "unfit" for surgery. Interestingly, one study that reported that 32% of included patients were unfit for surgery yet had a 93% 5-year survival rate which highlights how difficult predicting probable life expectancy can be [19]. Osborn and colleagues [15] in their study were the only authors to use a formal assessment of co-morbidity. They used the Charlson Index and reported that only 34% of their patients had a greater than 2% chance of surviving 10 years, with only 6 patients having a greater than 50% chance of surviving 10 years. The majority of

these six patients also had some form of dementia. Fourteen (17%) of the patients in this cohort eventually needed to undergo surgical treatment due to disease progression, and this was performed under local anaesthetic. Several of the studies also changed management at progression to surgical intervention, suggesting that their cohort was in fact fit for surgery at entry. This is one of the main problems with the original RCTs, in which patients had to be fit for surgery at randomisation and these are not the type of patients in whom PET is likely to be beneficial.

It must also be remembered when analysing the results of non-randomised studies that there is a great deal of heterogeneity in terms of the length of follow-up, type of PET or surgery, ER status, clinical assessment of response, patient fitness and co-morbid status and disease stage.

Both Bouchardy et al [56] and Ali et al [57] demonstrated that patients treated with surgery had better overall and breast cancer-specific survival, in keeping with the analysis of the non-randomised studies. There are several issues pertaining to quality of the data from the population-based studies which is inherent to all registry-based data, including selection bias due to unrecorded factors (for example if there are differences in assignment of patients to treatment [67], missing data that results from the coding process, as well as being non-randomised. Bouchardy et al [56] found that one third of patients in their population had no histological or cytological confirmation of diagnosis, which leads to issues with determining oestrogen positivity, and in Ali et al's study 18% had missing ER status [57]. Neither study examined the effect of co-morbidity on treatment assignment which clearly impacts on outcomes such as overall survival.

A recent questionnaire study in the UK demonstrated that the use of PET remains widespread in the UK, with 93% of 228 UK surgeons admitting to using it in early operable breast cancer, mostly for patients deemed unfit for surgery; however they also showed that 70% of respondents underestimated the average life-expectancy of an 80-year old women [10].

Conclusion

Primary endocrine therapy for breast cancer in elderly patients is popular in the UK, probably because it is a well-tolerated [69], simple treatment that avoids hospitalisation. Whilst there are many non-randomised studies suggesting a significant benefit of surgery in older women with breast cancer the evidence is unreliable due selection bias in these studies. Therefore the Cochrane review of the RCTs of surgery with or without endocrine therapy versus PET remains the most reliable guide to the use of PET in these patients although is not representative of actual current UK practice where older frailer women, with ER +ve disease will be selected. The evidence demonstrates an advantage for surgery in terms of disease control and a likely survival benefit in patients with minimal or moderate comorbidity and a predicted life expectancy of five or more years. However, all of the RCTs selected patients who were fit for surgery under general anaesthesia, a factor that makes these studies non representative of normal UK practice where PET tends to be used in women who are unfit for or of borderline fitness for surgery. Inevitably therefor these trials have found in favour of surgery due to the relatively longer life

expectancy of such women. In contrast for patients with a much reduced life expectancy (e.g. less than two years) due to substantial comorbidity, the benefit of surgery over PET may be much less relevant. Indeed subgroup analysis of data from 2 of the RCTs showed a survival advantage to surgery in women aged 70-75 but none in women over 75 [70]. Cohort study data shows that there is little difference in rates of BCSS between groups of women having PET or surgery using current selection criteria which is reassuring but guidelines to aid selection are urgently needed. If PET is to be used, this review has found that AIs provide superior rates of disease control compared to Tamoxifen and should be used unless contra-indicated.

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Tables:

Table 1: Characteristics of RCTs comparing PET with surgery

Study	n	PET type	Surgery	Age (years)	ER Status	Stage	Clinical Benefit Rate	Progressive Disease Rate	Failure Rate	Follow-up
Nottingham I, UK [26-29]	66	TAM	Wedge mastectomy, limited axillary surgery	≥70	Not assessed	I-II	**74%** CR 50%; PR 17%; SD 8%	26%	62%	Up to 21-27 years
Nottingham II, UK [30]	94	TAM	Wedge mastectomy, limited axillary surgery plus tamoxifen	78 (median)	All mod/ Strong ER +ve	I-II	**97%** CR 30%; PR 44%; SD 24%	3%	32%	Over 10 years
Naples, Italy [31]	37	TAM	Mastectomy or wide local excision plus tamoxifen	≥70	Not assessed	T1-3, N0-1	**73%** CR 14%; PR 22%; SD 38%	27%	35%	Over 10 years
GRETA, Italy [32]	235	TAM	Mastectomy or wide local excision with radiotherap	77 (median)	Not assessed	T1-3, N0-1	**99%** CR 9%; PR 32%; SD 55%	1%	45%	80 months

			y plus tamoxifen							
St Georges, UK [33,34]	100	TAM	Mastectomy or wide local excision without radiotherapy	75.5 (mean)	Not assessed	T1-4	NS	NS	25%	Up to 28 years
EORTC 10851, UK [35]	82	TAM	Mastectomy, full axillary clearance	76.3 (mean)	Not assessed	Upto T3, N1	NS	NS	68%	Up to 14 years
CRC, UK [36]	230	TAM	Mastectomy or wide local excision without radiotherapy plus tamoxifen	76 (median)	Not assessed	I-III	NS	NS	53%	Up to 16 years

[a]NS – Not stated; CR – Complete Response; PR – Partial Response; SD – Static Disease; TAM - Tamoxifen

Table 2a: Characteristics of Case Series/Cohort Studies that included patients regardless of ER status

Study	**n**	**PET type**	**Comparison**	**Age (years)**	**ER status**	**Stage**	**Clinical Benefit Rate**	**Progressive Disease Rate**	**Failure Rate**	**Follow-up (m)**
Gävle, Sweden [37]	27	TAM[¥]	None	80 (median)	NS	I-II	**93%** CR 56%; PR 22%; SD 7%	7%	19%	6-40
Dundee I, UK [6]	67	TAM[¥]	None	78.3 (mean)	NS	I-III	**73%** CR 27%; PR 21%; SD 25%	27%	31%	36
Newcastle, UK [38]	61	TAM[¥]	Surgery*	77 (median)	Unselected	70% stage I	**77%** CR 18%; PR 39%; SD 20%	23%	38%	14
Royal Marsden I, UK [39]	42	TAM[¥]	None	62 (mean)	NS	I-III	**95%** CR 2%; PR	5%	31%	19 (6-42)

							55%; SD 38%			
Mayday, UK [40]	51	TAM[¥]	None	78 (median)	NS	I-III	**54%** CR 18%; PR 24%; SD 12%	20%	NS	36
Southampton I, UK [41]	58	TAM[¥]	None	78.3 (mean*)*	NS	I-II	**69%** CR 17%; PR 17%; SD 35%	31%	66%	19
Edinburgh I, UK [42]	100	TAM[¥]	None	≥70	Unselected	I-IV	**90%** CR 40%; PR 28%; SD 22%	10%	NS	59
Florence, Italy [43]	62	TAM[¥]	None	78 (median)	NS	I-III	**96%** CR 11%; PR 40%; SD 45%	3%	31%	48
Southampton II, UK [44]	56	TAM[¥]	None	79 (median)	NS	I-III	**59%** CR 21%; PR 29%; SD 9%	29%	34%	60
Dundee II, UK [45]	113	TAM[¥]	None	70-93	Unselected	I-II	**79%** CR 34%; PR 15%; SD 30%	21%	62%	29 (1-103)
Radboud, Netherlands [46]	40	TAM[¥]	None	82.4 (mean)	Unselected	I-III	**82%** SD 40%	18%	NS	24

Nottingham I, UK [47]	50	NS	None	78 (mean)	Unselected	I-IIIa	**98%** CR 52%; PR 34%; SD 12%	2%	12%	28 (3-97)
NKI/DdHK, Netherlands [48]	84	TAM[¥]	None	83.6 (median)	Unselected	I-III	**85%** CR 14%; PR 24%; SD 46%	15%	44%	60
Royal Marsden II, UK [49]	54	TAM[¥]	None	83 (median)	Unselected	I-IV	**94%** CR 7%; PR 50%; SD 37%	6%	24%	23 (14-55)
Nottingham II, UK [50]	47	TAM[¥]	None	≥70	Unselected	NS	**83%** CR 4%; PR 30%; SD 49%	17%	NS	NS
Ireland [51]	68	TAM[¥]	None	≥70	Unselected	I-IV	**57%** SD 28%	31%	NS	NS
Tilberg, Netherlands [17]	113	TAM[¥]	Surgery*	83.5 (mean)	Unselected	NS	**62%**	2%	NS	49
Eindhoven, Netherlands [18]	184	TAM /AI	Surgery*	84 (mean)	Unselected	I-III	**58%** SD 11%	13%	35%	31 (1-102)

[b] *NS – Not stated; CR – Complete Response; PR – Partial Response; SD – Static Disease; TAM – Tamoxifen; AI – Aromatase Inhibitor*

Table 2b: Characteristics of Case Series/Cohort Studies that only included ER positive patients.

Study	n	PET type	Comparison	Age	ER status	Stage	Clinical Benefit Rate	Progressive Disease Rate	Failure Rate	Follow-up (m)
Edinburgh II, UK [52]	59	TAM[¥]	None	≥70	ER+	I-II	**54%** CR 24%; PR 22%; SD 8%	34%	46%	>6

Hull I, UK [53]	62	TAM /AI	Surgery *	80-98	ER+	NS	**60%**	NS	NS	20 (2-150)
Nottingham III, UK [54]	84/64	TAM¥	None	82.1 (mean)	ER+	NS	**100%** CR 8%; PR 18%; SD 74%	0%	NS	24 (6-72)
		ANZ¥					**97%** CR 9%; PR 30%; SD 58%	3%	NS	
Leicester, UK [55]	70	TAM¥	None	79 (median)	ER+	NS	**77%**	NS	84%	70 (9-119)
Luton, UK [13]	104	LET¥	None	83 (median)	ER+	NS	**82%** CR 23%; PR 40%; SD 18%	18%	37%	56 (4-106)
Sunderland, UK [14]	99	TAM /LET	Surgery *	84 (median)	ER+	NS	NS	NS	37%	76
Wales [15]	82	TAM /AI	None	81 (median)	ER+	NS	NS	NS	15%	24 (6-72)
Nottingham IV, UK [16]	616	TAM /AI	Surgery *	78 (median)	ER+	I-III	**84%** CR 26%; PR 30%; SD 29%	16%	45%	41 (1-202)
Queen Mary's, UK [19]	91	TAM /AI	None	80 (median)	ER+	I-IV	**78%** CR 17%; PR 45%; SD 16%	16%	NS	18 (2-70)
Hanover, Germany [20]	56	AI¥	None	74 (mean)	ER+	I-IV	**100%** CR 11%; PR 77%; SD 13%	0%	20%	51 (19-78)
Hull II, UK [21]	45	LET¥	None	87 (mean)	ER+	NS	**60%**	NS	NS	60
Valencia, Spain [22]	56	LET¥	None	79 (median)	ER+	I-III	**100%** CR 25%; PR 52%; SD 23%	0%	NS	12

*[c]NS – Not stated; CR – Complete Response; PR – Partial Response; SD – Static Disease; TAM – Tamoxifen; AI – Aromatase Inhibitor; LET – Letrozole; ANZ – Anastrozole; *denotes included in the comparison of PET vs Surgery; ¥ denotes included in the comparison of Tamoxifen vs AI.*