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Systematic Review

# Revisiting primary endocrine therapy *versus* surgery in older women with breast cancer: meta-analysis

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## Abstract

**Background:** Old age is associated with increased co-morbidities, resulting in reduced life expectancy. Primary endocrine therapy is an alternative to primary surgical therapy for patients with breast cancer and increased co-morbidities. The aim was to review outcomes of primary endocrine therapy *versus* primary surgical therapy in older women with breast cancer.

**Methods:** PubMed, Embase (Ovid), Scopus, and the Cochrane Library were searched systematically from January 2000 to May 2022. Single-arm studies were excluded. Primary outcomes were overall survival and breast cancer-specific survival. Secondary outcomes were local and regional failure of primary endocrine therapy, recurrence after primary surgical therapy, and health-related quality of life.

**Results:** There were 14 studies including 14 254 patients (primary endocrine therapy 2829, 19.8 per cent; primary surgical therapy 11 425, 80.2 per cent), with the addition of four major studies (9538 patients) compared with the latest review in 2014. Seven studies defined primary surgical therapy as surgery plus adjuvant endocrine therapy, and six studies included patients with oestrogen receptor-positive tumours only. Patients in the primary endocrine therapy group were older than the primary surgical therapy group (mean difference 2.43 (95 per cent c.i. 0.73 to 4.13) years). Primary endocrine therapy led to worse overall survival than primary surgical therapy (HR 1.42, 95 per cent c.i. 1.06 to 1.91). Subgroup analysis of RCTs and prospective studies, however, showed comparable overall survival. Breast cancer-specific survival was also comparable (HR 1.28, 95 per cent c.i. 0.87 to 1.87). At 6 weeks, operated patients had significant arm symptoms and illness burden following major breast surgery compared with patients receiving primary endocrine therapy. Health-related quality of life, measured by the European Organization for Research and Treatment of Cancer QLQ-C30 and EuroQol EQ-5D-5L™, was comparable in the two treatment groups.

**Conclusion:** Overall survival was worse among older women receiving primary endocrine therapy in an analysis including all studies, but comparable in RCTs and prospective studies. This may be due to confounding by age and co-morbidities in retrospective cohort studies of primary endocrine therapy.

## Introduction

Female breast cancer has the highest incidence of cancers worldwide, and represents 11.7 per cent of all cancers diagnosed in 2020[1]. Despite having the highest incidence, it is only the fifth leading cause of cancer death worldwide, with 685 000 deaths[1]. Advances in technology and healthcare have resulted in improved life expectancy, with an increase of 0.9 years for men and 0.8 years for women per decade at the age of 60 years[2]. In Singapore, the proportion of citizens aged 65 years and over has increased from 10.4 per cent in 2011 to 17.6 per cent in 2021, and is expected to reach almost one-quarter (23.8 per cent) by 2030[3]. The median age at breast cancer diagnosis has increased to 61 years in the USA[4], and from 57.9 years in 1968 to 62.9 years in 2019 in Singapore[3]. The ageing breast cancer population necessitates treatment optimization in older women.

Old age is associated with a reduction in vital capacity, lean body mass, reduced cardiac output, and sarcopenia[5]. Age is also associated with increased co-morbidities and frailty, leading to higher risk during general anaesthesia as well as higher rates of postoperative morbidity, longer hospital stay, and increased mortality[6]. Surgery remains the mainstay treatment for breast cancer. Unlike some oncological surgery with high perioperative risks[7], breast surgery has a low 30-day postoperative mortality rate. As an example, the prospective Bridging the Age Gap in Breast Cancer study[8] showed no 30-day mortality among 2854 women aged at least 70 years. Surgery may also result in impaired quality of life (QoL), especially with ipsilateral arm complications, including pain, numbness, and lymphoedema. Hence, non-surgical options have been offered, such as first-line primary endocrine therapy (PET) with tamoxifen (TAM) or aromatase inhibitors (AIs)[9–11]. A systematic review by Morgan *et al.*[12] in 2014, which included 6 non-RCTs with 3559 patients, showed that overall survival (OS) was significantly higher with primary surgical therapy (PST) than with PET (67 *versus* 49 per cent; $P < 0.01$). The authors concluded that PET should be reserved for patients with a predicted life expectancy of less than 5 years. Apart from survival, QoL is also an important consideration in the decision-making

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process[13]. PET has been shown to be tolerable with few treatment-related side-effects, and does not bear the additional complications from breast surgery, such as lymphoedema and arm pain[13–15].

This study aimed to provide an updated systematic review and compare long-term oncological outcomes and health-related QoL (HRQoL) between PET and PST in older women with breast cancer.

## Methods

This systematic review and meta-analysis of previously conducted studies does not contain any new studies with human participants or animals performed by any of the authors. Hence, no ethical approval was required.

### Study selection and search strategy

This systematic review compared the clinical outcomes between PET and PST in older women aged at least 65 years with breast cancer. It was performed according to the PRISMA guidelines and checklist (*Table S1*)[16] and was registered at PROSPERO (CRD42022351691). A systematic search of published articles in peer-reviewed journals was performed in PubMed, Embase (Ovid), Scopus, and the Cochrane Library from 1 January 2000 to 14 May 2022. The search was limited to articles published after 2000, as a preliminary search identified a large number of irrelevant articles at earlier time points. Nevertheless, cross-referencing was done with existing meta-analyses by Hind *et al.*[17] in 2007 and Morgan *et al.*[12] in 2014 to ensure inclusion of all related studies in the present systematic review. A combination of search terms ('breast cancer' or 'breast malignancy') and ('aged' or 'geriatrics' or 'elderly' or 'old*') and ('surgery' or 'breast conserving surgery' or 'mastectomy') and ('endocrine therapy' or 'tamoxifen' or 'aromatase inhibitor') was used. The detailed search strategy is available in *Table S2*.

Inclusion criteria were RCTs and non-RCTs comparing clinical outcomes and QoL between PET and PST in women diagnosed with breast cancer aged 65 years or more. Exclusion criteria were: studies not relevant to breast cancer; single-arm studies on PET or PST alone; breast cancer in men; review articles, letter to editors, editorials or conference abstracts; non-English language articles and articles without full texts; and articles with overlapping cohorts (only the later publication was included unless otherwise specified). Varying definitions of older age have been used in the literature, ranging from 65 to 80 years. Traditionally, older is defined as at least 65 years old[18]. For the purpose of this study, older patients were defined as those aged 65 years and over to ensure inclusion of more articles. PST was defined as the use of surgery alone or surgery plus adjuvant endocrine therapy (ET), whereas PET comprised primary treatment with ET and omission of surgery.

After removal of duplicates, two authors independently screened the studies by title and abstract for potential inclusion in the study. Full texts of all eligible articles were subsequently reviewed and assessed based on the inclusion and exclusion criteria. Conflicts were resolved by consensus or by appeal to the senior author. The entire study selection process is reflected in the PRISMA flow diagram (*Fig. S1*).

### Data extraction

Two authors independently undertook the data extraction from the included studies. The following variables were extracted from each study: publication details (name of first author, year of study, study interval, country of study, study design), study characteristics (size, definition of older, type of PET and/or PST, oestrogen receptor (ER) status, and duration of follow-up). Studies that used a combination of therapies were classified under the predominant therapy if this was used in at least 90 per cent of patients (for example, if TAM or AI was used, and less than 10 per cent of patients received AI, the study was classified as TAM only). The primary outcomes were OS, breast cancer-specific survival (BCSS), and HRQoL. OS was defined as the proportion of patients alive at the end of the study or follow-up, whichever was earlier. Five-year BCSS was defined as the proportion of patients who had not died from breast cancer by 5 years after initiation of PET or PST. HRQoL was defined by the impairment, functional states, perceptions, and social opportunities influenced by disease or its associated treatment[19]. Secondary outcomes were recurrence-free survival (RFS), local control (defined as local failure for PET and local recurrence for PST), regional control (defined as regional failure for PET and regional recurrence for PST), distant metastasis, and failure of treatment when a change in management was required. Other outcome measures were reported for PET, including clinical benefit, complete response, partial response, stable disease, and progression of disease. Definitions were in accordance with UICC criteria[20].

### Assessment of study quality

Quality assessment was undertaken using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) for RCTs (*Table S3*)[21], and the modified Newcastle–Ottawa scale for observational studies (*Table S4*)[22]. Level of evidence was graded using the Oxford 2011 Levels of Evidence by Oxford Centre for Evidence-Based Medicine[23].

### Statistical analysis

Study variables were extracted and tabulated in Microsoft® Excel 365 (Microsoft, Redmond, WA, USA). Categorical variables were described as numbers with percentages, and continuous variables as median (range) or mean(s.d.), as reported in the original studies. For observational studies that used propensity score matching, only data from the propensity score-matched (PSM) cohort were collected and analysed unless otherwise specified. For studies that expressed data only as median with range or i.q.r., mean(s.d.) values were estimated using methods described by Wan *et al.*[24] for quantitative analysis. For studies that only provided the mean with *P* value, methods described by Lee *et al.*[25] were used to derive mean(s.d.) values. For analysis of cumulative OS and BCSS, hazard ratio (HR) and standard error (s.e.) were estimated indirectly according to the methods described by Parmar *et al.*[26]. Pooled HRs for survival outcomes (OS, BCSS, and RFS) were calculated using the natural logarithm of HR (ln(HR)) and s.e. and the DerSimonian–Laird method[27]. Continuous variables were analysed using the DerSimonian–Laird method (for random effects) and expressed as a weighted mean difference (MD) with 95 per cent confidence interval. Pooled analyses were not performed for recurrence, metastasis or response rates as cumulative data were not available in the original studies. Heterogeneity was assessed using Cochrane's Q and quantified by means of the $I^2$ value. A random-effects model was used for all outcome variables in view of sampling variability owing to inclusion of different study types. Statistical significance was defined as $P < 0.050$. Publication bias was investigated using funnel plots and Egger's regression test[28]. Subgroup analyses for OS and BCSS was performed for type of study (RCT, prospective cohort study, or retrospective cohort study). Subgroup analysis was also carried out for RFS based on the type of recurrence (local, regional or distant metastasis). Sensitivity analyses were conducted for statistically significant results to

estimate the effect size by serial exclusion of individual studies. Meta-analysis was performed using Stata® version 17.0 (StataCorp, College Station, TX, USA).

## Results

A total of 3234 articles were identified using the search strategy. After removal of duplicates, 2456 articles were retrieved. Subsequently, 98 full-text articles were assessed for eligibility based on the inclusion and exclusion criteria. A total of 14 articles[29–42] were included in the final quantitative analysis (*Fig. S1*). There were five RCTs[29–33], three prospective cohort studies[34,41,42], and six retrospective studies[35–40]. Of the prospective cohort studies, those by Morgan *et al.*[41] and Wyld *et al.*[42] included propensity score matching, as did the retrospective study by Suen *et al.*[40]. Morgan *et al.*[41] and Wyld *et al.*[42] reported outcomes for the same cohort of patients in the Bridging the Age Gap in Breast Cancer study. Results from both studies were included as they discussed separate outcomes (QoL outcome measures *versus* oncological outcomes). Demographics were, however, recorded from only one article as both studies involved the same cohort. Two studies[43,44] had later publications on the same cohort of patients. The newer studies were by Johnston *et al.*[29] in 2012 (Nottingham 2 trial) and Chakrabarti *et al.*[30] in 2011 (Nottingham 1 trial), which replaced the study by Willsher *et al.*[44], as well as a newer study by Fennessy *et al.*[33] in 2004 (Cancer Research Campaign) that replaced the study by Bates *et al.*[43]. The results reported by Bates *et al.* were, however, included (though not in the quantitative analysis) as they reported PET response and QoL outcome measures, which were not reported by Fennessy *et al.* The study published by van der Plas-Krijgsman *et al.*[45] in 2022 was excluded; although it included two cohorts (Bridging the Age Gap in Breast Cancer study and Climb Every Mountain study),

**Table 1 Characteristics of included studies comparing primary endocrine therapy and primary surgical therapy**

| Reference | Type of study | Study interval | Definition of older (years) | No. of patients | | Treatment | | | ER status (positive) | Longest follow-up (median) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | PET | PST | PET | PST | Adjuvant ET | | |
| Johnston *et al.*[29] | RCT | 1989–1996 | ≥ 70 | 100 | 53 | TAM 20 mg OD | Mx | All patients | All positive | 20 years (78 months) |
| Chakrabarti *et al.*[30] | RCT | 1982–1987 | > 70 | 65 | 66 | TAM 20 mg BD | Wedge Mx | No | n.r. | 20 years |
| Mustacchi *et al.*[31] | RCT | Mar 1987 to Jun 1992 | ≥ 70 | 235 | 239 | TAM 160 mg day 1, then 20 mg OD | n.r. | All patients | PET: n.r. PST: 72% | 13 years (80 months) |
| Gazet and Sutcliffe[32] | RCT | 1982–1989 | > 70 | 100 | 100 | TAM 20 mg OD | BCS, Mx | No | All positive | 28 years |
| Fennessy *et al.*[33] | RCT | 1984–1991 | ≥ 70 | 230 | 225 | TAM 40 mg OD | BCS, Mx, modified Mx | All patients | n.r. | 12.7 years |
| Bates *et al.*[43]* | RCT | n.r. | ≥ 70 | 183 | 171 | TAM | BCS or Mx | All patients | n.r. | 34 months* |
| Nicholson *et al.*[34] | PCS | n.r. | ≥ 60 | 61 | 33 | TAM 20 mg OD or low-dose aminoglutethimide 125 mg BD (4.9%) + hydrocortisone 20 mg BD | n.r. | No | PET: 60% PST: 67% | 5 years (14 months) |
| Traa *et al.*[35] | RCS | 1985–2005 | ≥ 75 | 113 | 233 | TAM | n.r. | Yes (52.4%) | PET: 91.2% PST: 69.6% | PET: 4.1 years PST: 6.5 years |
| Wink *et al.*[36] | RCS | 2001–2008 | ≥ 75 | 184 | 1504 | TAM (55%), AI (45%) | n.r. | n.r. | PET: 94.2% PST: n.r. | 8.5 years (2.6 years) |
| Rao *et al.*[37] | RCS | 1992–2002 | ≥ 80 | 62 | 48 | TAM (87.1%), AI (12.9%) | BCS (37.5%), Mx (62.5%) | Yes (93.8%) | PET: 94.7% PST: 71.4% | 154 months (41 months) |
| Syed *et al.*[38] | RCS | 1973–2009 | ≥ 70 | 449 | 616 | TAM or AI | BCS, Mx | Yes; 50% in BCS, 61.6% in Mx | All positive | PET: 16.8 years PST: 19.2 years (49 months) |
| Nayyar *et al.*[39] | RCS | 1 Jan 2008 to 31 Dec 2013 | ≥ 70 | 778 | 8006 | TAM or AI | n.r. | All patients | Either ER- or PR-positive | n.r. |
| Suen *et al.*[40] | RCS, PSM† | 2008–2017 | ≥ 70 | 83 | 209 | TAM (55%), AI (45%) | BCS, Mx, radical Mx | All patients | All positive | (67.2 months) |
| Morgan *et al.*[41] | PCS, PSM† | Feb 2013 to June 2018 | ≥ 70 | 238 | 422 | TAM (4.4%), AI (90.4%), unknown (5.2%) | BCS or Mx + ALND +/− CT +/− RT +/− ET | All patients | All positive | (52 months) |
| Wyld *et al.*[42] | PCS, PSM† | Jan 2013 to Jun 2018 | | | | | | | | |

*This study was not included in the quantitative analysis as a newer study was performed by Fennessy *et al.*[33] in 2004. It is reported here as it included the clinical response to primary endocrine therapy (PET) that was not included in the newer study. †Only data from the propensity score-matched (PSM) cohort are included. PST, primary surgical therapy; ET, endocrine therapy; ER, oestrogen receptor; TAM, tamoxifen; OD, once a day dosing; Mx, mastectomy; BD, twice a day dosing; n.r., not reported; BCS, breast-conserving surgery; PCS, prospective cohort study; RCS, retrospective cohort study; AI, aromatase inhibitor; PR, progesterone receptor; ALND, axillary lymph node dissection; CT, chemotherapy; RT, radiotherapy.

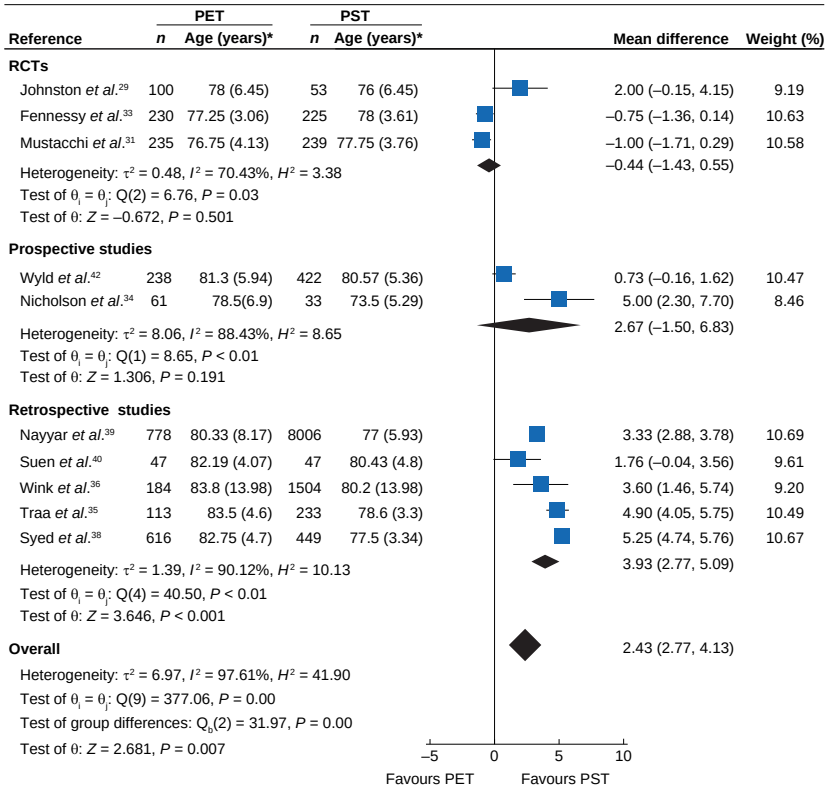


**Fig. 1 Forest plot comparing age of included patients in primary endocrine therapy and primary surgical therapy groups**

*Values are mean(s.d.). Mean differences are shown with 95% confidence intervals. A random-effects DerSimonian–Laird model was used for meta-analysis. PET, primary endocrine therapy; PST, primary surgical therapy.

the main purpose of the study was to compare outcomes between the two cohorts without a comparison between PET and PST. The study published by Husain *et al.*[46] in 2008 described HRQoL after PET or PST, and was excluded as it was a qualitative cross-sectional study of a small group of 21 patients who were surveyed at varying times after diagnosis. The study by Dordea *et al.*[47] was also excluded as it compared conservative management *versus* surgery, without all of the patients in the conservative group receiving ET. Funnel plots are shown in *Fig. S2*. None of the study outcomes showed significant publication bias in Egger's regression test, except for RFS ($P = 0.027$).

## Study characteristics

There were 14 studies including a total of 14 254 patients (PET 2829, 19.8 per cent; PST 11 425, 80.2 per cent), with 4 major studies comprising 9538 patients added compared with the latest review in 2014 by Morgan *et al.*[12]. Study characteristics are summarized in *Table 1*. The median study interval was 8 (range 5.25–36) years. In the PST group, seven studies[29,31,33,39–42] included surgery with adjuvant ET in all patients, three[35,37,38] included surgery with ET in some patients, three[30,32,34] included surgery alone, and one study[36] did not report whether adjuvant ET was used. Patient demographics and tumour characteristics in included studies are summarized in *Table S5*. Mean age ranged from 76.8 to 83.8 years among patients who received PET, and from 77.8 to 80.6 years in those who had PST. Age was significantly higher in the PET group (MD 2.43 (95 per cent c.i. 0.73 to 4.13) years; $P = 0.007$). Subgroup analysis, however, showed comparable age in RCTs and prospective studies, whereas patients were significantly older in the PET group compared to the PST group in retrospective studies (*Fig. 1*). Six studies[29,32,38,40–42] included only patients with ER-positive tumours, of which two[41,42] described the same cohort of patients (Bridging the Age Gap in Breast Cancer study).

## Survival

Seven studies[29,33,35–37,39,40] reported 5-year OS, and five[29,33,35,37,40] reported 10-year OS (*Table 2*). Median 5-year OS was 59.5 (6.3–78.0) per cent for PET and 67.4 (52.1–89.6) per cent for PST. Median 10-year OS rates were 24.7 (1.6–64.0) and 37.7 (12.9–66.0) per cent respectively. Median reported OS ranged from 42.0 to 73.0 months for PET, and from 70.9 to 74.0 months for PST[30,31,37]. The pooled analysis showed that PET had worse cumulative OS than PST (HR 1.42, 95 per cent c.i. 1.06 to 1.91; $P = 0.020$) (*Fig. 2a*). Sensitivity analysis did not show any individual study with a dominant effect. Subgroup analysis, however, showed comparable OS between PET and PST both for RCTs (HR 1.12, 0.97 to 1.28; $P = 0.123$) and prospective studies (HR 2.15, 0.26 to 17.83; $P = 0.479$) (*Fig. 2a*). A subgroup analysis for studies that only included ER-positive tumours was not undertaken owing to the small number of studies that reported OS outcomes and ER status (2 RCTs, 1 prospective study, 1 retrospective study)[29,32,40,42].

A subgroup analysis of adjuvant ET was undertaken. OS was lower for PET than for PST plus adjuvant ET (*Fig. 2b*). OS was comparable for PET and PST when there was no adjuvant ET after surgery. A subgroup analysis based on presence of adjuvant ET in retrospective studies only, however, showed significantly worse OS

**Table 2 Summary of overall survival and breast-cancer specific survival in included studies**

| Reference | Overall survival | | | Breast cancer-specific survival | | |
|---|---|---|---|---|---|---|
| | PET<br>Median (months)<br>5 years (%)<br>10 years (%) | PST<br>Median (months)<br>5 years (%)<br>10 years (%) | Comparison | PET<br>Median (months)<br>5 years (%)<br>10 years (%) | PST<br>Median (months)<br>5 years (%)<br>10 years (%) | Comparison |
| Johnston *et al.*[29] | –<br>74.0<br>64.0 | –<br>83.0<br>66.0 | 5 years: $P = 0.206$<br>10 years: $P = 0.802$ | –<br>92<br>89 | –<br>92.5<br>86.8 | 5 years: $P = 0.921$<br>10 years: $P = 0.687$ |
| Chakrabarti *et al.*[30] | 73.0<br>–<br>– | 74.0<br>–<br>– | $P = 0.446$ | – | – | – |
| Mustacchi *et al.*[31] | 71.2<br>–<br>– | 70.9<br>–<br>– | Unadjusted RR 1.02 (0.8, 1.3; $P = 0.89$) | – | – | Unadjusted RR 1.38, (0.94, 2.04; $P = 0.09$) |
| Gazet and Sutcliffe[32] | – | – | Unadjusted HR 1.3 (1.05, 1.60) | – | – | Unadjusted HR 1.68 (1.15, 2.47) |
| Fennessy *et al.*[33] | –<br>59.5<br>28.8 | –<br>67.4<br>37.7 | Adjusted HR 1.3 (1.05, 1.60) | – | – | Unadjusted HR 1.68 (1.15, 2.47) |
| Nicholson *et al.*[34] | – | – | n.s. | – | – | – |
| Traa *et al.*[35] | –<br>41.0<br>5.1 | –<br>61.8<br>27.8 | 5 years: $P = 0.421$*<br>10 years: $P = 0.324$* | –<br>85<br>79.5 | –<br>87.3<br>78.3 | Adjusted HR 0.68 (0.33, 1.42)<br>5 years: $P = 0.421$*<br>10 years: $P = 0.324$* |
| Wink *et al.*[36] | –<br>27.0<br>– | –<br>62.3<br>– | $P < 0.001$ | – | – | – |
| Rao *et al.*[37] | 42.0<br>6.3<br>1.6 | 71.0<br>52.1<br>12.9 | Stage I–II: $P < 0.001$<br>Stage III–V: $P = 0.03$ | – | – | – |
| Syed *et al.*[38] | – | – | – | Not reached<br>84<br>– | Not reached<br>95<br>– | 5 years: $P < 0.001$ |
| Nayyar *et al.*[39] | –<br>78.0<br>– | –<br>89.6<br>– | Adjusted HR 1.69 (1.35, 2.13) | –<br>95.3<br>– | –<br>98.2<br>– | Adjusted HR 1.92 (1.11, 3.33) |
| Suen *et al.*[40] | –<br>70.0<br>24.7 | –<br>70.6<br>61.5 | 5 years: $P = 0.63$<br>10 years: $P = 0.003$ | – | – | – |
| Morgan *et al.*[41]<br>Wyld *et al.*[42] | – | – | Adjusted HR 1.39 (1.02, 1.89; $P = 0.037$) | – | – | Adjusted HR 1.35 (0.73, 2.50; $P = 0.34$) |

Values in parentheses are 95% c.i. HR: Hazard ratio; PET, primary endocrine therapy; PST, primary surgical therapy; RR, risk ratio; n.s., not significant. *Reflects the difference in both overall survival and breast cancer-specific survival between PET and PST.

after PET compared with PST regardless of whether adjuvant ET was given (*Fig. 2c*). Furthermore, a subgroup analysis based on type of PET (TAM only, AI only, or TAM or AI) showed worse OS after PET in the AI-only and TAM or AI subgroups. However, in the six studies in which patients received TAM only, OS was comparable to that after PST (HR 1.12, 0.96 to 1.30; $P = 0.151$) (*Fig. 2d*).

Four studies[29,35,38,39] reported 5-year BCSS, and two[29,35] reported 10-year BCSS (*Table 2*). Median 5-year BCSS was 88.5 (84.0–95.3) and 93.8 (87.3–98.2) per cent for PET and PST respectively. Median 10-year BCSS was 84.3 (79.5–89.0) per cent for PET and 82.6 (78.3–86.8) per cent for PST. Pooled analysis showed comparable BCSS between PET and PST (HR 1.28, 0.87 to 1.87; $P = 0.209$). A subgroup analysis according to study design showed similar results in RCTs, and prospective and retrospective studies (*Fig. 3a*).

Pooled analysis showed worse RFS for PET compared with PST (HR 2.11, 1.34 to 3.33; $P = 0.001$) (*Fig. 3b*). In terms of location of the relapse, subgroup analysis showed worse local RFS for patients in the PET group (HR 3.26, 2.20 to 4.82; $P < 0.001$). However, for studies reporting on regional RFS or unspecified RFS, the outcome was comparable between PET and PST. Event-free survival (with event defined as local or regional recurrence, progression, presence of distant metastasis, or death) was reported to be significantly worse after PET compared with PST (median event-free survival 40 *versus* 61.6 months; $P < 0.001$)[31].

## Failure, recurrence, and response

Three studies[29,33,35] reported local failure or recurrence. The median 5-year local failure/recurrence rate was 38.0 (17.0–64.0) per cent for PET and 6.0 (1.9–10) per cent for PST, excluding the study by Fennessy *et al.*[33]. That study reported local recurrence/failure based on type of surgery, noting that the local recurrence rate was 8 per cent for mastectomy and 18 per cent for breast-conserving surgery. Gazet and Sutcliffe[32] reported a median time of 13.5 months to local recurrence/failure for both PET and PST. Chakrabarti *et al.*[30] reported a median time of 25 months to local failure for PET, whereas the median was not reached for PST even at the end of follow-up.

One study[29] reported 5- and 10-year regional failure/recurrence. The outcomes were comparable for PET and PST regarding 5-year (8 *versus* 5.7 per cent respectively; $P = 0.594$) and 10-year (9 *versus* 7.5 per cent; $P = 0.759$) regional failure/recurrence. One study[30]

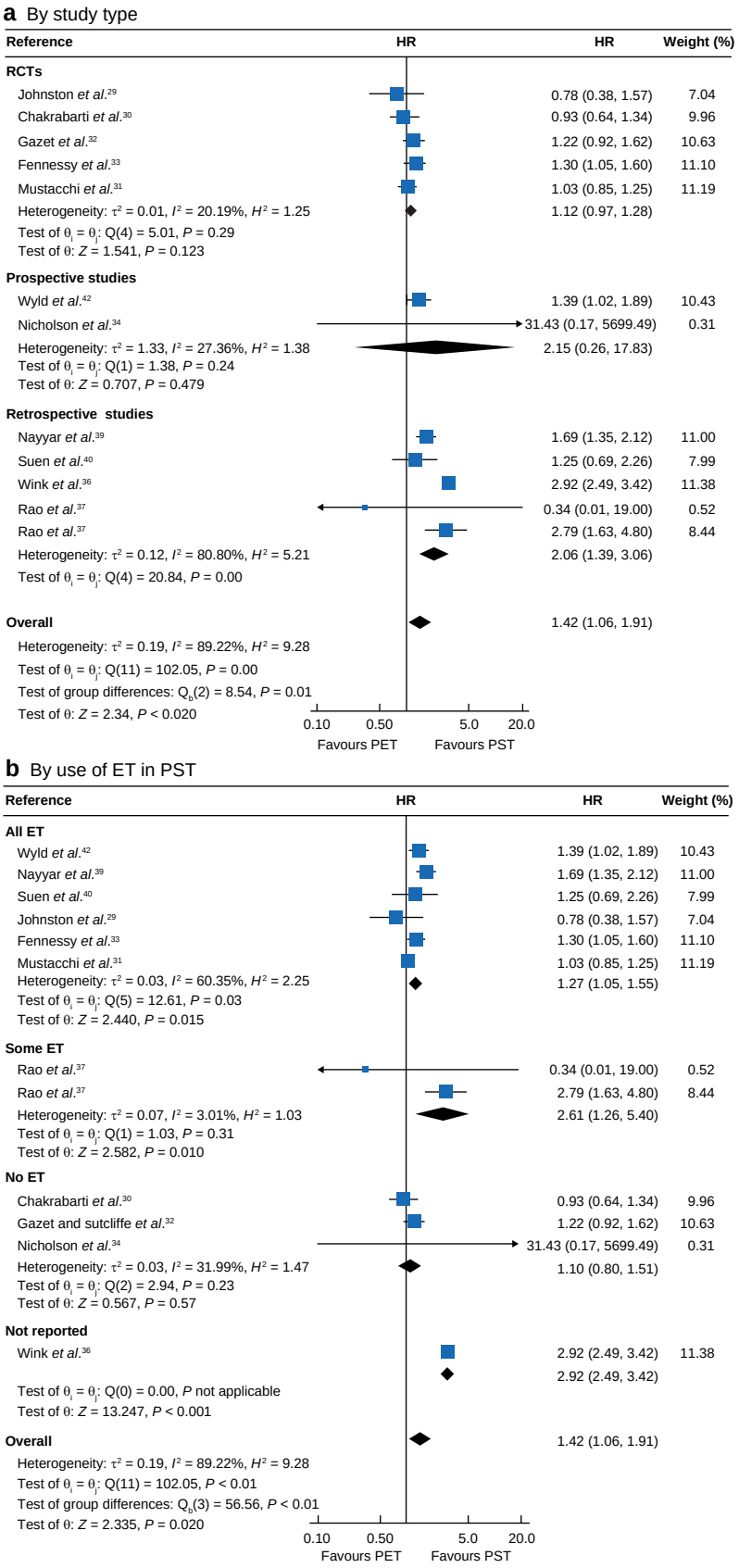


**Fig. 2 Forest plot comparing overall survival between primary endocrine therapy and primary surgical therapy, with subgroup analyses based on study type and use of adjuvant endocrine therapy**

**a** By study type, **b** by use of adjuvant endocrine therapy (ET) in primary surgical therapy (PST), **c** by use of adjuvant ET in PST in retrospective studies only, and **d** by type of ET. HRs are shown with 95% confidence intervals. A random-effects DerSimonian–Laird model was used for meta-analysis. PET, primary endocrine therapy; TAM, tamoxifen; AI, aromatase inhibitor.

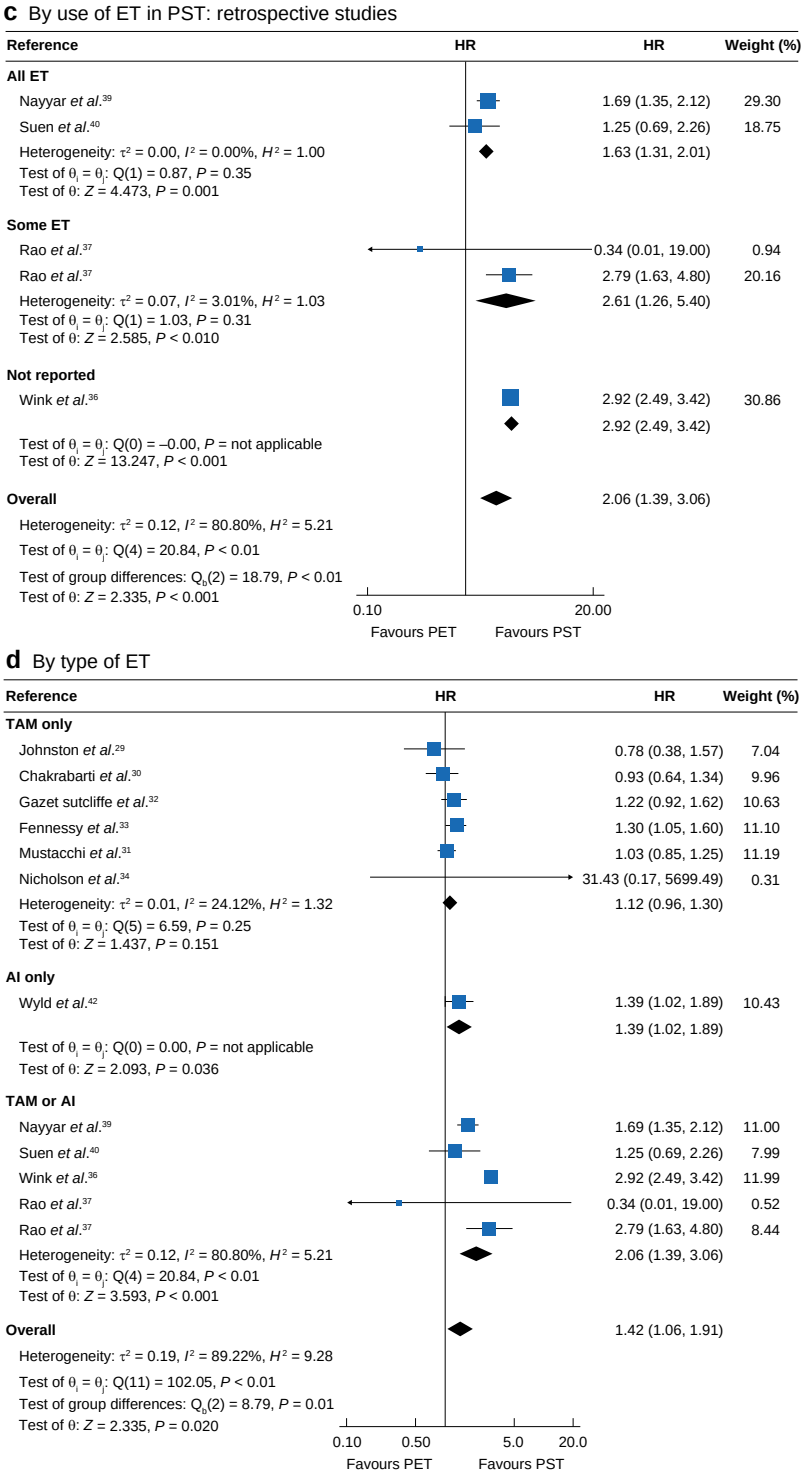


**Fig. 2** Continued

reported a median time to regional failure/recurrence of 107 months for PET and 100 months for PST ($P = 0.511$).

Eight studies reported on distant metastasis, five RCTs[29–33] and three observational studies[35,37,38]. None of the RCTs found a significant difference in distant metastasis rates between PET and PST. Of the three observational studies, Traa *et al.*[35] reported a significantly higher incidence of distant metastases in the PET group compared with the PST group at 2-, 5-, and 10-year follow-up. Two studies[29,35] reported 5- and 10-year distant metastasis rates (*Table S6*). Johnston *et al.*[29] reported comparable 5-year (PET 8.0 per cent *versus* PST 7.4 per cent; $P = 0.762$) and 10-year (8.0 *versus* 13.2 per cent respectively; $P = 0.303$) distant metastasis rates. Traa *et al.*[35], however, showed higher 5-year (37.0 *versus* 23.0 per cent; $P = 0.03$) and 10-year (83.0 *versus* 49.5 per cent; $P = 0.001$) rates of distant metastases for PET.

Five studies reported on response to PET (*Table S7*). The median 6-month rate of clinical benefit was 96.4 (77.1–97.9) per cent. Median 6-month complete response, partial response, and stable

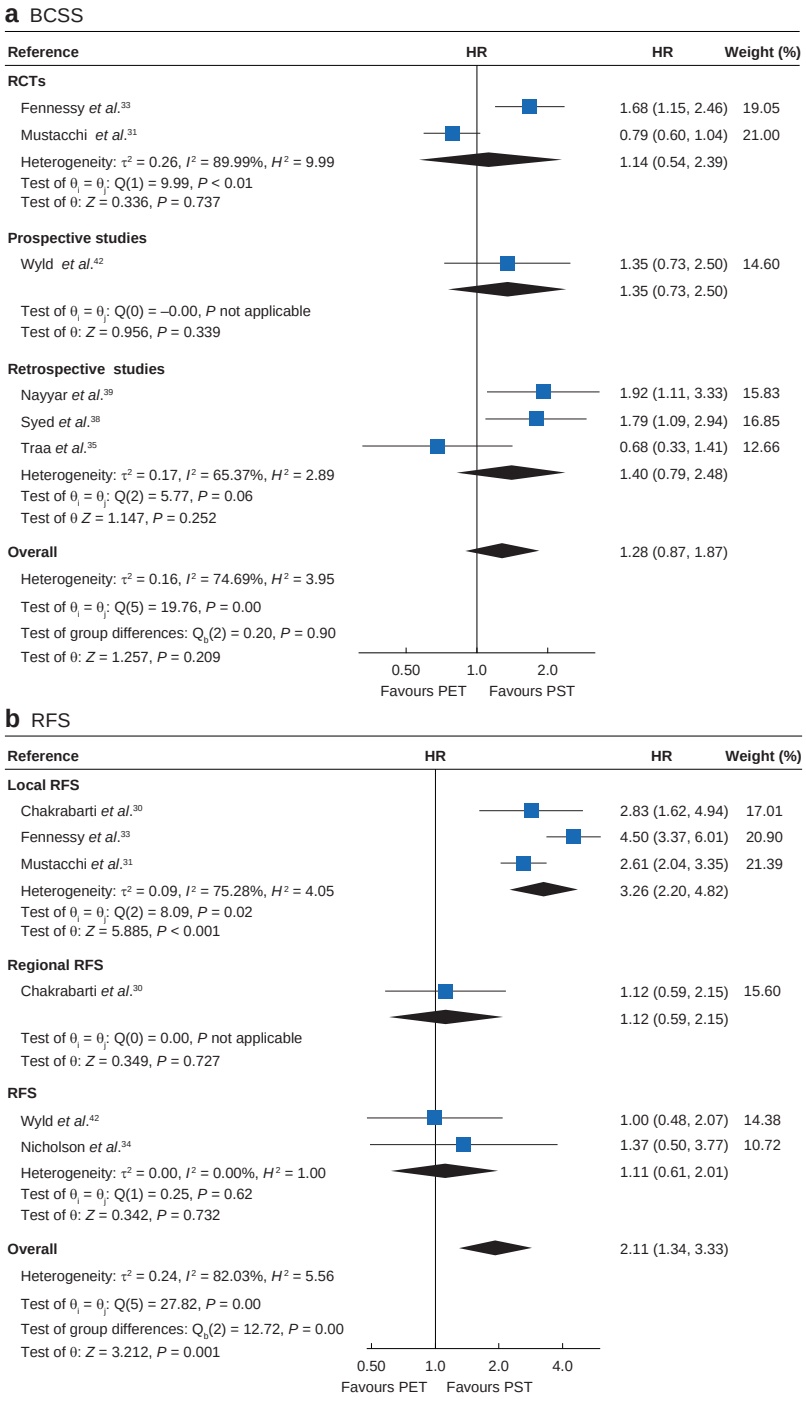


**Fig. 3 Forest plot comparing breast-cancer specific survival with subgroup analysis based on study type, and recurrence-free survival with subgroup analysis by type of recurrence, between primary endocrine therapy and primary surgical therapy**

**a** Breast-cancer specific survival (BCSS) and **b** recurrence-free survival (RFS). HRs are shown with 95% confidence intervals. A random-effects DerSimonian–Laird model was used for meta-analysis. PET, primary endocrine therapy; PST, primary surgical therapy.

disease rates were 14.2 (9.2–28), 37.3 (9–47), and 49.0 (19.7–62.6) per cent respectively. The median rate of progression of disease was 3.3 (0.8–23) per cent. Nine studies[29,30,33,35–39,43] reported on the failure of treatment, that is disease progression necessitating a change in management. For patients who received PET, a median of 42.0 (35–62.6) per cent required a change to second-line treatment, 15.5 (3.2–40.4) per cent required salvage surgery, and 32.5 (18.3–41.2) per cent required a change in ET (*Table S8*). Only three studies[29,33,43] reported on failure of treatment requiring change in management for PST, with a median of 20.5 (range 13–31.6) per cent needing a change to second-line treatment.

## Health-related quality of life

Three studies[41–43] reported HRQoL, two of which described the same cohort of patients (Bridging the Age Gap in Breast Cancer study); while both the studies by Morgan *et al.*[41] and Wyld *et al.*[42] reported on HRQoL, the study by Wyld *et al.*[42] was excluded

from the qualitative synthesis of HRQoL as the primary aim of their study was on long-term survival outcomes rather than HRQoL (this was the primary aim of the study by Morgan *et al.*[41] instead). In a cohort of 237 patients (PET 120, PST 117), Bates *et al.*[43] showed no significant difference in ability to manage household tasks (inability to manage household tasks: 44 of 120 (36.7 per cent) in PET group; 36 of 117 (30.8 per cent) in PST group). They also used the General Health Questionnaire (GHQ) 28, and showed no significant difference in physical malaise, anxiety, social dysfunction, and depression between PET and PST[43]. Mean time between treatment and administration of the questionnaire was similar for PET and PST (12 (range 3–32) *versus* 13.5 (3–33) months).

Morgan *et al.*[41] studied 660 patients aged at least 70 years (PSM cohort; PET 238, PST 422), and analysed QoL using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (generic cancer questionnaire), EORTC QLQ-BR23 (breast cancer-specific questionnaire), EORTC QLQ-ELD15 (HRQoL in older population), and the EuroQol Five Dimensions Five Level (EQ-5D-5L™; EuroQol Group, Rotterdam, the Netherlands) questionnaire. Their main findings were worse arm symptoms at 6 weeks following intervention for patients who underwent major breast surgery compared with PET (MD 8.85, 95 per cent c.i. 3.63 to 14.07), measured using the EORTC QLQ-BR23. Arm symptoms were also worse after minor breast surgery although less than after major breast surgery, but did not reach statistical significance (MD 1.77, −3.59 to 7.12). The EORTC QLQ-ELD15 also showed a significantly higher burden of illness following major breast surgery compared with PET (MD 7.57, 0.58 to 14.56), whereas the results were comparable for minor breast surgery *versus* PET (MD 5.17, −1.99 to 13.32). There were no significant differences in domains assessed using the EORTC QLQ-30 and EQ-5D-5L™.

## Discussion

PST remains the mainstay treatment option for breast cancer. Although breast surgery is associated with a low postoperative mortality rate[8], there are postoperative complications that can impair QoL. PET is an alternative treatment for older women with multiple co-morbidities.

The last systematic review comparing PET *versus* PST, published by Morgan *et al.*[12] in 2014, included seven RCTs and six non-RCTs. The conclusion was that PET was associated with worse OS and RFS. The present study provides an important addition to the previous meta-analysis, and included 4 new and major studies (2 prospective cohort studies with PSM, 1 retrospective study with PSM, and 1 unmatched retrospective study) with an additional 9538 patients (PET 1063, PST 8475). The present meta-analysis also used pooled HRs (ideal for time-to-event outcomes such as survival) to compare OS, BCSS, and RFS between PET and PST by extraction of data from published Kaplan–Meier curves using methods described by Parmar *et al.*[26].

The present findings were similar to those of Morgan *et al.*[12], with worse OS and RFS for PET compared with PST based on a pooled analysis, but comparable BCSS. Sensitivity analysis did not reveal a dominant effect of an individual study that could have biased the results. There are a few explanations for worse OS, yet comparable BCSS between PET and PST. There is inherent selection bias in non-RCTs, with older patients opting for PET instead of PST because of their greater perioperative risks. For instance, in the retrospective study by Wink *et al.*[36], the mean age of the PET group was 83.8 years compared with 80.2 years in the PST group ($P < 0.001$). Pooled analysis of age across the studies also showed that patients receiving PET were older than those who had PST (MD 2.43 (95 per cent c.i. 0.73 to 4.13) years). This is further reinforced by the finding that BCSS was similar for PET and PST. Hence, worse OS in PET was possibly due to non-cancer-related deaths among patients who were older, with worse physiological reserve and more co-morbidities[5]. Subgroup analysis based on study design also showed that patients were older in the PET group in retrospective studies, but comparable between the two groups in RCTs and prospective studies. In line with this, OS was comparable for PET and PST in RCTs and prospective cohort studies. Unfortunately, the majority of the included studies did not report on co-morbidities and it was not possible to compare patient demographics in more detail. Another possible confounding factor for worse OS in PET in retrospective studies could be the inclusion of ER-negative tumours, as these have been shown to have progression rates of up to 100 per cent[31,48–51]. The majority of the retrospective studies, however, included only patients with ER-positive tumours.

This study demonstrated comparable BCSS between PET and PST, a result that is unlikely to be affected by sample size. Although only 6 studies reported BCSS, 11 784 patients were included (PET 2210, PST 9574). This is only 12.7 per cent less than the number of patients included in the analysis of OS (12 studies with 13 503 patients overall; PET 2338, PST 11 165). Moreover, the majority of included patients (8784 patients) were from the retrospective study by Nayyar *et al.*[39], which showed that PET only was independently associated with worse BCSS than PST plus adjuvant ET (adjusted HR 1.92, 95 per cent c.i. 1.11 to 3.33).

The present study demonstrated worse RFS for PET compared with PST, which is similar to the finding of Morgan *et al.*[12]. Clinical benefit rates in ER-positive breast cancer have been shown to be high, with an overall reduction in size or failure to progress in 75 per cent of patients[17,52]. It has been argued that findings of higher rates of recurrence/progression of disease may be due to inclusion of ER-negative tumours[12,31,48–51]. The studies included in the present review had a high median 6-month clinical benefit rate (96.4 (range 77.1–97.9) per cent), with a low median rate of disease progression at 6 months (3.3 (0.8–23) per cent). Mustacchi *et al.*[31] noted that the time to best response was 5.1 (95 per cent c.i. 3.7 to 6.5) months. Syed *et al.*[38] additionally reported that patients with clinical benefit at 6 months had significantly better BCSS than those whose disease progressed ($P < 0.001$). It is important to note, however, that the number of patients with progressive disease was small (11 of 515, 2.1 per cent). In addition, Gazet and Sutcliffe[32] reported a median time of 13.5 months to local recurrence/failure in both PET and PST, whereas Chakrabarti *et al.*[30] reported a median time of 25 months to local failure in PET, but the median was not reached for PST. Although the rate of clinical benefit was high at 6-month follow-up, it is possible it may decrease later, resulting in worse RFS in the PET group.

The meta-analysis by Hind *et al.*[52] in 2006 showed no difference between surgery and PET, and between surgery plus adjuvant ET and PET. It is important to note that, when surgery plus adjuvant ET was compared with PET, there was a trend towards improved survival in the surgery plus adjuvant ET group with near statistical significance [Peto odds ratio (OR) 0.86, 95 per cent c.i. 0.73 to 1.00; $P = 0.056$], whereas surgery alone was comparable to PET (Peto OR 0.98, 0.74 to 1.30; $P = 0.90$). The present study similarly showed worse OS for PET *versus* surgery plus adjuvant ET, but comparable

OS between PET and surgery without adjuvant ET. Five years of adjuvant ET in early-stage ER-positive breast cancer has been shown to reduce breast cancer-specific mortality by one-third[53].

A meta-analysis including 31 920 postmenopausal women who received adjuvant ET by the Early Breast Cancer Trialists' Collaborative Group[54] in 2015 showed that AIs reduced recurrence rates by about 30 per cent more than TAM. A subgroup analysis of OS based on type of PET received (TAM only, AI only, and TAM or AI) was undertaken in the present work, but the results were inconclusive as only one study[42] compared the use of AI *versus* surgery plus adjuvant ET. Comparison between primary TAM and AI *versus* surgery was also not possible as no subgroup analysis was performed in the original studies. Evidence has shown that AI is superior to TAM in terms of survival outcomes after surgery[54]. This effect has, however, not been explored when comparing PET with PST. Only one study, by Wink *et al.*[36], compared the use of TAM *versus* AIs (letrozole, anastrozole or exemestane) in 184 patients receiving PET, and showed no differences in time to response ($P = 0.487$) and progression ($P = 0.498$) between the groups.

Another important consideration when deciding treatment options especially for older patients is quality *versus* quantity of life, that is survival. Surgery carries perioperative risks, general postoperative complications, as well as surgery-specific postoperative complications, for example ipsilateral arm complications such as pain[55]. Husain *et al.*[46] conducted a qualitative cross-sectional interview of 21 patients who received either PET or mastectomy at various time points following diagnosis. Interestingly, both PET and PST groups described satisfaction with their treatment options with little disturbance in their lives. The present systematic review included two studies[41,43] that described HRQoL. Bates *et al.*[43] showed no difference between PET and PST groups in the ability to manage household tasks nor any difference in psychosocial morbidity using the GHQ-28 score. Morgan *et al.*[41] demonstrated significantly worse arm symptoms and burden on daily life 6 weeks after major breast surgery compared with PET, but no significant effects were noted for minor breast surgery. This emphasizes the importance of preoperative optimization with dedicated geriatric perioperative pathways, surgical services, and prehabilitation to improve postoperative outcomes in older patients[56,57].

Cost-effectiveness, which is rarely reported in the literature, should also be considered. A recent study by Holmes *et al.*[58], from the Bridging the Age Gap in Breast Cancer study, reported that surgery was more cost-effective than PET, except for a small subgroup of patients age 90 years or over with a co-morbidity score of 2 or 3, regardless of nodal status.

This study has some strengths. It is an updated systematic review and meta-analysis with a large sample size reporting on the outcomes of PET *versus* PST. It is also the first to use data from reported Kaplan–Meier curves for calculation of the pooled HR, which is superior to the OR or risk ratio, as HR is a measure of effect for time-to-event outcomes, such as survival. QoL outcome measures that were not previously reported were also included in the present analysis. There are, however, limitations. The search strategy was limited to begin from 2000 and could have missed earlier studies. The population was heterogeneous in terms of age, only one study was conducted in an Asian population, and not all studies reported on ER status and baseline co-morbidities. Breast cancers in men were also excluded in view of differences in management. There were also only two studies that assessed HRQoL.

Older women who receive PET have worse OS and RFS than those who undergo PST. This may, however, be confounded by increased age and co-morbidities in patients receiving PET. HRQoL was mostly comparable between PET and PST, except in the immediate postoperative phase for patients who underwent major breast surgery. PST should be recommended for older women who are fit for surgery. Patients should be counselled adequately on the advantages and disadvantages of each option as the extent of informed consent has been shown to be inadequate in the older population[59]. This is a pertinent issue as the treatment options vary, with differences in oncological outcomes and QoL reported. Further well designed standardized RCTs should be carried out to validate these findings and explore the use of AIs compared with primary surgery.

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## Supplementary material

Supplementary material is available at *BJS* online.

## Data availability

Data were collected and tabulated from all the included studies. Requests for availability of the data may be made to the corresponding author.

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