



Defer surgery in operable breast cancer: how long is too long?

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Abstract

Purpose The aim of this meta-analysis was to evaluate outcomes of surgery compared to primary endocrine therapy (PET) in patients with non-advanced, operable invasive breast cancer, and to determine if PET as initial therapy may safely postpone surgery.

Methods The MEDLINE, EMBASE, PubMed, and Cochrane Library were searched from database inception to July 2020 to identify eligible studies. Inclusion criteria were experimental or observational studies with at least one arm treated with PET and a second arm treated with surgery with or without PET. Local recurrence or progression of disease was defined as either failure of non-operative management (tumor failing to decrease in size and/or continuous local or distant tumor growth) or relapse of breast tumor after tumor downsizing following PET. Effect estimates were expressed in hazard ratio and 95% confidence intervals (HR (95% CI)).

Results The analysis included six studies with 1499 unique patients. The median time to local progression of disease was 2.3 years. Patients treated with PET alone without surgery had a higher risk of local recurrence and or progression [HR (95% CI): 1.76 (1.33, 2.31); $I^2 = 84%$; $p < 0.001$]. Patients treated with PET had more favorable outcomes in terms of overall survival [HR (95% CI): 1.24 (1.06, 1.46); $I^2 = 70%$; $p = 0.008$] and less favorable outcomes in breast cancer-specific survival [HR (95% CI): 1.13 (0.98, 1.31); $I^2 = 41%$; $p = 0.10$]. The risk of publication bias was assessed to be high in reporting local recurrence rates and low in reporting distant recurrence rates.

Conclusion PET alone is inferior to surgery in the treatment of operable invasive breast cancer. However, it may be acceptable to postpone curative breast cancer surgery without risk of progression for 1.1 years or longer.

Keywords Breast cancer · Surgery · Endocrine therapy · Tamoxifen · COVID-19

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated disease (COVID-19) has majorly impacted the distribution of healthcare resources around the world [1]. This has significantly altered how patients are screened and treated for recently diagnosed breast cancer. On March 26, 2020, the American Society of Breast Surgeons filed a joint statement with the American College of Radiology stating that all breast screening exams, including mammography, ultrasound, and MRI, were to be temporarily suspended until the COVID-19 pandemic

is better controlled [2]. Similarly, patients currently undergoing treatment for diagnosed breast cancer (BC) are also experiencing disrupted medical care [3]. In a survey that was completed by 377 breast care providers from large institutions and university affiliated hospitals in 41 different countries, 34% reported a reduction in their overall workload by $\geq 50%$, and 13% indicated that breast care was relocated to reduce hospital visits [4].

The standard of care for patients diagnosed with localized breast cancer consists of a combination of surgery, radiation therapy, and systemic therapy [5]. However, various groups, including the National Comprehensive Cancer Network, recently published guidelines that support adjusted or delayed treatment plans for patients diagnosed with breast cancer during these unprecedented times [3, 6, 7]. One recommendation is the use of primary endocrine therapy (PET) as first line treatment preoperatively rather than definitive breast surgery. PET may be an attractive option for

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luminal-like tumors as it could minimize hospital admissions and delay elective surgeries [7]. Therefore, it is not surprising that in the aforementioned survey, 68% of responders considered initial endocrine treatment in patients diagnosed with hormone receptor-positive breast cancer with the intent to postpone surgery [4].

Approximately 75% of breast cancers are hormone receptor (HR)-positive, indicating estrogen receptor (ER) and progesterone receptor (PR) tumor expression [8]. Tamoxifen, fulvestrant, and aromatase inhibitors are the most common endocrine therapies used to treat breast cancer in both the neoadjuvant and adjuvant settings [9]. Though the gold standard of care for initial treatment of localized, early-stage breast cancer is surgery, there are various situations, in addition to suspension of elective and non-emergent surgery, for which PET may be the preferred first course of treatment. PET is often the preferred treatment for early-operable breast cancer if patients are elderly and unfit for surgery [10]. PET is also used as initial course of treatment to downstage primary breast tumor burden to aid in future resection [11].

Over the past few decades, the increasing use of PET as a preoperative, initial treatment for breast cancer instead of surgery has generated various studies comparing the long-term outcomes of patients who undergo solely endocrine therapy versus surgery. In 2010, a Cochrane review summarized the findings of seven studies on this topic, and they concluded that primary endocrine therapy is inferior to surgery with endocrine therapy for the local control of breast cancer in ER-unselected, medically fit older women [12]. However, since publication, various other groups have come forward with additional data, with some claiming that patients with ER-rich tumors do equally well on PET as compared to surgery [13]. The aim of this meta-analysis was to amalgamate all studies that have assessed the outcomes of PET versus surgery for patients diagnosed with early breast cancer to provide comprehensive evidence on the benefits or risks of PET in place of surgery. In turn, this study would delineate the possible long-term implications of treating early-operable breast cancer patients with solely PET when surgery is prohibited and reserved for only emergent procedures. Further, insight may be given on long-term delay or omission of surgery for local treatment of otherwise operable breast cancer.

Materials and methods

Study design, search strategy, and research question

This systematic review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [14]. In July 2020, a systematic search of studies in

PubMed, Ovid MEDLINE, and Embase was performed based on guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [16]. The protocol of this systematic review was developed a priori and published [17]. Following MeSH terms were used for the literature search: ‘breast cancer’, ‘endocrine therapy’, ‘surgery’ combined with the Boolean operator ‘AND’ and all synonyms combined with the Boolean operator ‘OR’. The research question was formulated within the PICOT(S) framework as follows:

(P) Population: Adults older than 18 years with breast cancer.

(I) Intervention: Primary endocrine therapy.

(C) Comparator: Surgery.

(O) Outcomes: local and/or distant recurrence (progression), overall and cancer-specific survival, all-cause and cancer-specific mortality.

(T) Timing: Long-term.

(S) Setting: In- and outpatient.

Eligibility criteria, endpoints, and definitions

Inclusion criteria are any experimental or observational design study comparatively evaluating long-term outcomes of PET and surgery for breast cancer. Studies comparing one of the interventions of interest to a non-relevant intervention, descriptive studies, and summary design studies were excluded. The primary endpoint of this review was local and distant cancer recurrence or progression of disease, local or distant. Secondary endpoints included overall and cancer-specific survival as well as all-cause and cancer-specific mortality. Local recurrence or progression of disease was defined as either failure of non-operative management whereby the tumor does not decrease in size, has continuous local or distant tumor growth, or recurs in the breast after tumor downsizing or disappearance of tumor following PET. In other words, local recurrence and progression were defined as any situation when either the primary breast cancer did not respond to the treatment, i.e., size did not change or increased, or regrowth of tumor after a period of time that it had disappeared. Progression of disease was also defined as occurrence of disease in axillary lymph nodes or distant organs when uninvolved on initiation of PET, regardless of the status of response of the primary breast cancer to the treatment.

Study selection and data extraction

After removing the duplicates, screening of all titles, abstracts, and full-text articles of potentially eligible studies was performed by two reviewers (SR and AR) working independently and in duplicate. Any disagreements at full-text

screening were resolved by consensus. Data extraction of each eligible study was also performed independently and in duplicate by the same two reviewers. Following variables were extracted and inserted in predefined Microsoft Excel tables: authors, year and journal of publication, study ID, study design, baseline characteristics, and oncological outcomes.

Statistical analysis

The risk of bias was assessed by reviewers working independently and in duplicate using the Cochrane assessment tool for RCTs. Disagreements were resolved by consensus. A meta-analysis of hazard ratios (HR) was performed in two stages. The log-rank Observed minus Expected events ($O-E$) as well as the log-rank Variance (V) were estimated for each included individual study using randomization ratio, numbers of randomized and analyzed patients, number of events, and follow-up details (employing direct or indirect methods). A fixed effect model of $\text{Exp}[O-E]/\text{Var}$ method was utilized for the meta-analysis of hazard ratios. Effect estimates were expressed in HRs with corresponding 95% confidence intervals (HR (95%CI)). Statistical heterogeneity was evaluated with the χ^2 test, and inconsistency was estimated using the I^2 statistic [18]. The risk of publication bias was evaluated through visual assessment of symmetry on the funnel plots of HR and standard error of logHR. Statistical analysis was conducted using Review Manager (RevMan; version 5.1 for Mac; Nordic Cochrane Centre, Cochrane Collaboration; Copenhagen, Denmark).

Results

A total of 12,708 potential studies were identified by the systematic search. Of these, 1,133 titles were selected for abstract screening. Of the 1133 screened abstracts, 39 full-text manuscripts were assessed for eligibility. Ultimately, a total of six randomized controlled trials were selected, with 1499 unique patients. The PRISMA flow diagram detailing the study selection process is shown in Fig. 1. The findings of quality assessment are depicted in risk of bias summary and graph (Fig. 2). Overall bias risk was found to be low.

Study characteristics

Characteristics of the included studies were summarized in Table 1. The six selected studies [19–24] were published from 2000 to 2011. The sample sizes ranged from 75 to 474 and all consisted of women ≥ 70 years old diagnosed with breast cancer. The selected studies compared surgery (typically mastectomy) \pm tamoxifen vs. PET (typically

tamoxifen). Additional details on the selected studies are shown in Table 2.

Local and distant recurrence (progression) rates

Patients treated with PET had a higher risk of local recurrence [HR (95% CI): 1.76 (1.33, 2.31); $I^2 = 84\%$; $p < 0.001$] yet a decreased risk of distant recurrence [HR (95% CI): 0.76 (0.59, 0.98), $I^2 = 0\%$; $p = 0.04$] (Fig. 3). The way each study defined local and distant recurrence is outlined in Table 1. The median time to local recurrence was assessed for the PET arm of each study to elucidate how long it may be safe to treat patients with solely PET to postpone surgery. Five [20–24] of the selected studies plus one additional study [25] that was only included in the qualitative analysis reported on time to local disease progression. Time to local disease progression for patients treated with solely PET ranged from 1.1 [22] to 5.8 [25] years, with four studies reporting median time to local progression of 1.7 [21], 2.1 [20], 2.5 [24], and 3.3 [23] years from the initiation of endocrine therapy.

Overall and cancer-specific survival rates

Patients treated with PET had more favorable outcomes in terms of overall survival as compared to those treated with surgery \pm PET with considerable among-study statistical heterogeneity [HR (95% CI): 1.24 (1.06, 1.46); $I^2 = 70\%$; $p = 0.008$]. However, breast cancer-specific survival rates did not significantly differ between PET and surgery \pm PET with moderate heterogeneity [HR (95% CI): 1.13 (0.98, 1.31); $I^2 = 41\%$; $p = 0.10$] (Fig. 4).

All-cause and cancer-specific mortality rates

All-cause [HR (95% CI): 1.09 (0.97, 1.24); $I^2 = 76\%$; $p = 0.16$] and cancer-specific mortality rates [HR (95% CI): 1.11 (0.91, 1.36); $I^2 = 64\%$; $p = 0.31$] did not significantly differ between patients treated with PET and those treated with surgery \pm PET with substantial among-study statistical heterogeneity (Fig. 5).

Subgroup meta-analysis

A subgroup meta-analysis was performed after excluding studies, in which the comparator arm was surgery alone. The findings of local and distant recurrence rates were not significantly different in the subgroup meta-analysis (Supplements 1 and 2). Overall [HR (95% CI): 1.17 (0.99, 1.38); $I^2 = 58\%$; $p = 0.07$] and breast cancer-specific survival rates [HR (95% CI): 1.13 (0.96, 1.33); $I^2 = 67\%$; $p = 0.13$] did not significantly differ between the arms (Supplements 3 and 4). All-cause mortality rates favored surgery \pm PET [HR (95% CI): 1.21 (1.05, 1.40); $I^2 = 0\%$; $p = 0.01$], whereas

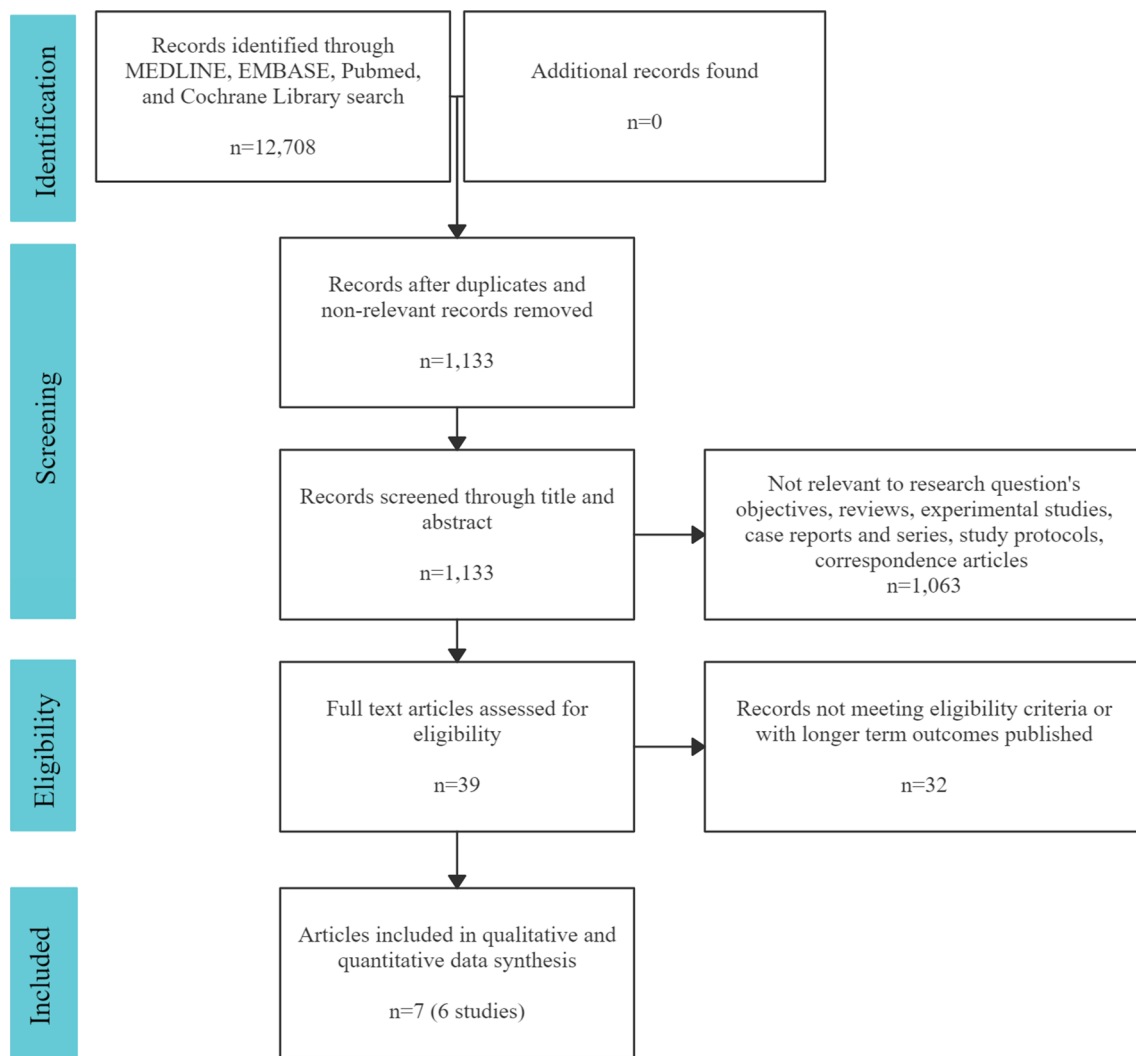


Fig. 1 PRISMA flow diagram

cancer-specific mortality rates [HR (95% CI): 1.21 (0.96, 1.52); $I^2 = 65\%$; $p = 0.10$] did not significantly differ between the arms (Supplements 5 and 6).

Publication bias

The risk of publication bias was assessed to be high in reporting local recurrence rates and low in reporting distant recurrence rates (Fig. 6).

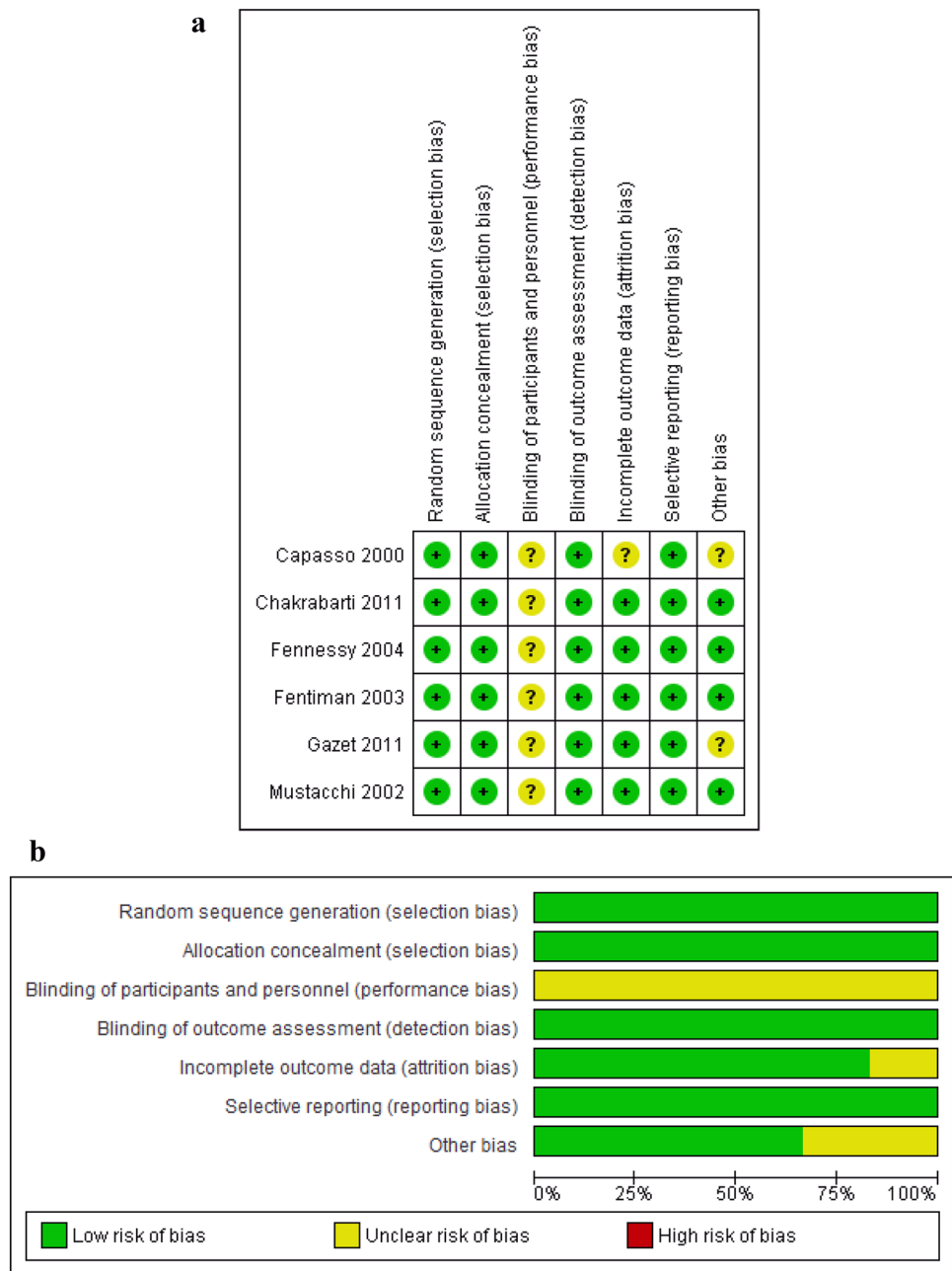
Discussion

Cancer care was severely impacted by the COVID-19 pandemic. Significant reductions in clinical activity delayed cancer operations to preserve resources and protect patients and staff. The normal operating cadre is a mix of emergent,

urgent and elective cases. In phase 1 of the pandemic, elective cases were removed, most semi-urgent cases were postponed, and in pandemic hot spots, urgent cases were also delayed [26]. This ultimately led to an enormous backlog of patients at the end of the surge that required operations.

In the United States, 1.8 million patients are diagnosed with cancer each year [27]. Therefore, during 3-month pandemic window, this equates to 150,000 new cancer cases per month. Acute disruption in the ability to deliver care for approximately 3 months during the height of the pandemic affected nearly 0.5 million patients diagnosed with cancer during the peak phase of SARS-CoV-2 virus outbreak. Of those 1.8 M new cancer diagnoses, almost half are screen detectable [28]. Throughout the pandemic, among the many stages of cancer care that were delayed, screening evaluations had significant impact [2]. Though several of the larger cancer organizations, such as ASCO, SSO, and ASBrS,

Fig. 2 a Risk of bias summary.
b Risk of bias graph



developed guidelines to try to preserve critical screening and surveillance, screening began to decline very early on in the pandemic, several months prior to the surge. According to IQVIA utilization data, there was a severe reduction in mammograms performed well before cessation at the height of the pandemic [29]. Surveillance and office visits were also decreased, as screening was low.

Overall, the diagnosis of new breast cancer cases during the peak of COVID-19 was impacted not only by low screening rates, but also by prior cases that were delayed in treatment. The potential impact due to the buildup of overdue screening is enormous and more than initially anticipated.

As we emerge from COVID-19, the recovery phase may not be just that. We are tasked with conducting care while the pandemic threats are still present. As we go forward to protect surgical patients from exposure and possible infection while elective surgeries have restarted, we look to prior efforts to prioritize care.

The main results of this meta-analysis show that PET alone was inferior to surgery combined with or without PET. Patients treated with surgery are at decreased risk for local recurrence with higher rates of both overall and breast-cancer-specific survival, and lower rates of both cancer-specific mortality and all-cause mortality. Though these outcomes

Table 1 Description of included studies

Study ID	Journal	Study design	Details of treatment	Sample size		Sample size by arm		Definition of local progression		Length of Follow up (months)		Level of evidence
				Surgery	ET	Surgery	ET	Surgery	ET	Surgery	ET	
Capasso 2000	Annals of Oncology	RCT	Mastectomy + Tamoxifen 20 mg/day	Tamoxifen 160 mg day 1 followed by 20 mg/day	75	38	37	NR	NR	121	123	1b
Chakrabarti 2011	Critical Reviews in Onc/Hem	RCT	Wedge mastectomy	Tamoxifen 20 mg BID	131	66	65	Recurrence in ipsilateral chest wall following mastectomy	Local disease progression	240	240	1b
Fennessy 2004	British Journal of Surgery	RCT	Mastectomy or local excision + tamoxifen 40 mg/day	Tamoxifen 40 mg/d	455	225	230	NR	NR	148.8	154.8	1b
Fentiman 2003	Eur J Cancer	RCT	Modified radical mastectomy	Tamoxifen 20 mg/day	164	82	82	Local skin, axillary recurrence or regional node involvement	Progression of the primary tumor and/or increase in size by > 25% of axillary nodes, occurrence of new axillary nodes, or regional node invasion	140.4	122.4	1b
Gazet 2011	Journal of Cancer Surgery	RCT	Wide local excision or mastectomy + tamoxifen 20 mg/day if nonmetastatic recurrence	Tamoxifen 20 mg/day	200	100	100	Local progression or local recurrence as a first event without evidence of distant metastases	Local progression or local recurrence as a first event without evidence of distant metastases	336	336	1b
Mustacchi 2002	Annals of Oncology	RCT	Mastectomy + tamoxifen 20 mg/day	Tamoxifen 160 mg day 1 followed by 20 mg/day	474	239	235	Local progression of the ipsilateral breast or other locoregional	Local progression of the ipsilateral breast or other locoregional	79.6	80.1	1b

Table 2 Demographics and cancer-specific variables of the included studies

Study ID	Age		Lymph nodes		Cancer stage	
	Surgery	ET	Surgery	ET	Surgery	ET
Capasso 2000	NR	NR	NR	NR	NR	NR
Chakrabarti 2011	> 70	> 70	NR	NR	< 4 cm ² : 18 2–9 cm ² : 24 – 16 cm ² : 21 – 25 cm ² : 2	< 4 cm ² : 13 2–9 cm ² : 35 – 16 cm ² : 16 – 25 cm ² : 2
Fennessy 2004	76	76	No palpable: 179 Palpable: 40 Not known: 6	No palpable: 191 Palpable: 33 Not known: 6	T1: 48 T2: 114 T3a: 9 T4b: 54	T1: 38 T2: 130 T3a: 16 T4b: 46
Fentiman 2003	> 70	> 70	N0: 59 N1A: 8 N1B: 14 Unknown: 1	N0: 57 N1A: 11 N1B: 14 Unknown: 0	T1: 14 T2: 57 T3: 9 T4: 1 Unknown: 1	T1: 12 T2: 56 T3: 12 T4: 1 Unknown: 1
Gazet 2011	76.9	75.4	NR	NR	T1: 22 T2: 48 T3: 23 T4: 7	T1: 17 T2: 52 T3: 17 T4: 14
Mustacchi 2002	76	77	N0: 136 N1a: 69 N1b: 27 N3: 1 Unknown: 6	N0: 150 N1a: 66 N1b: 15 N3: 0 Unknown: 4	< 2cm: 135 2–5 cm: 96 > 5cm: 2	< 2 cm: 127 2–5 cm: 101 > 5 cm: 3

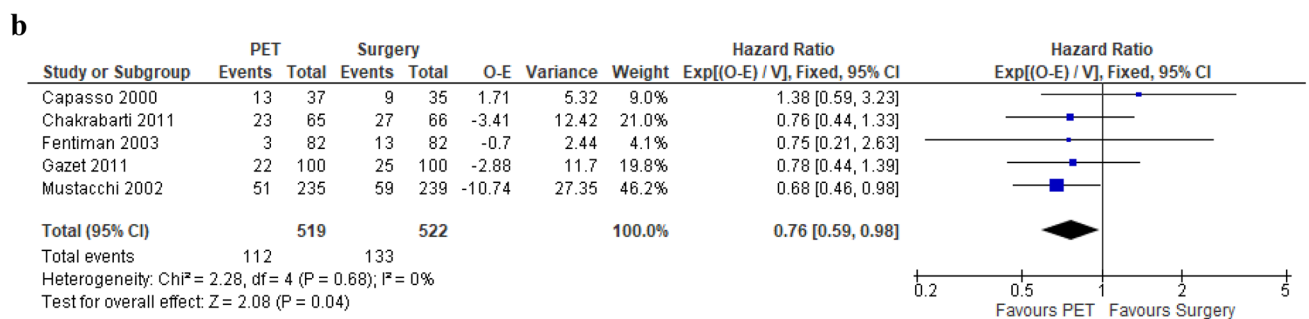
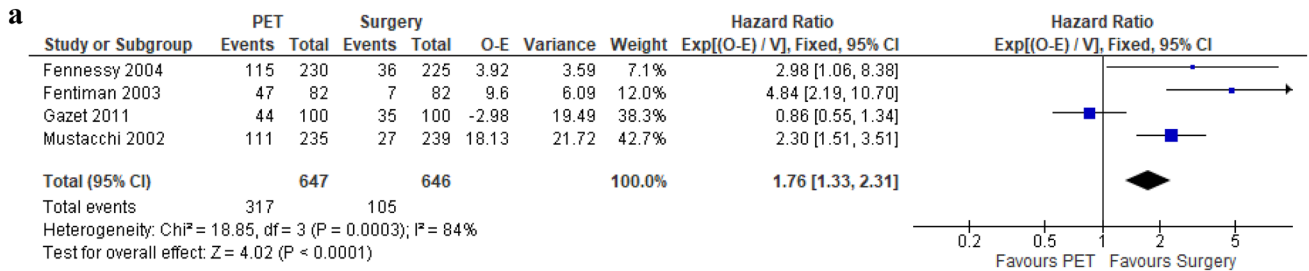


Fig. 3 Forest plots comparing PET and surgery: **a** local recurrence (progression) rates. **b** Distant recurrence (progression) rates

support upfront surgery in treating patients diagnosed with early breast cancer, these studies also shed light onto a potential window of time that may be acceptable to treat patients with PET in an effort to postpone surgery.

How long is too long? Of the six studies that reported on time to local recurrence, the mean time to local

progression was 2.8 years from the initiation of endocrine therapy (range: 1.1–5.8 years). Therefore, it may be acceptable to treat patients with PET alone for this time period of 2.8 years before undergoing surgery without local recurrence. However, a conservative approach for

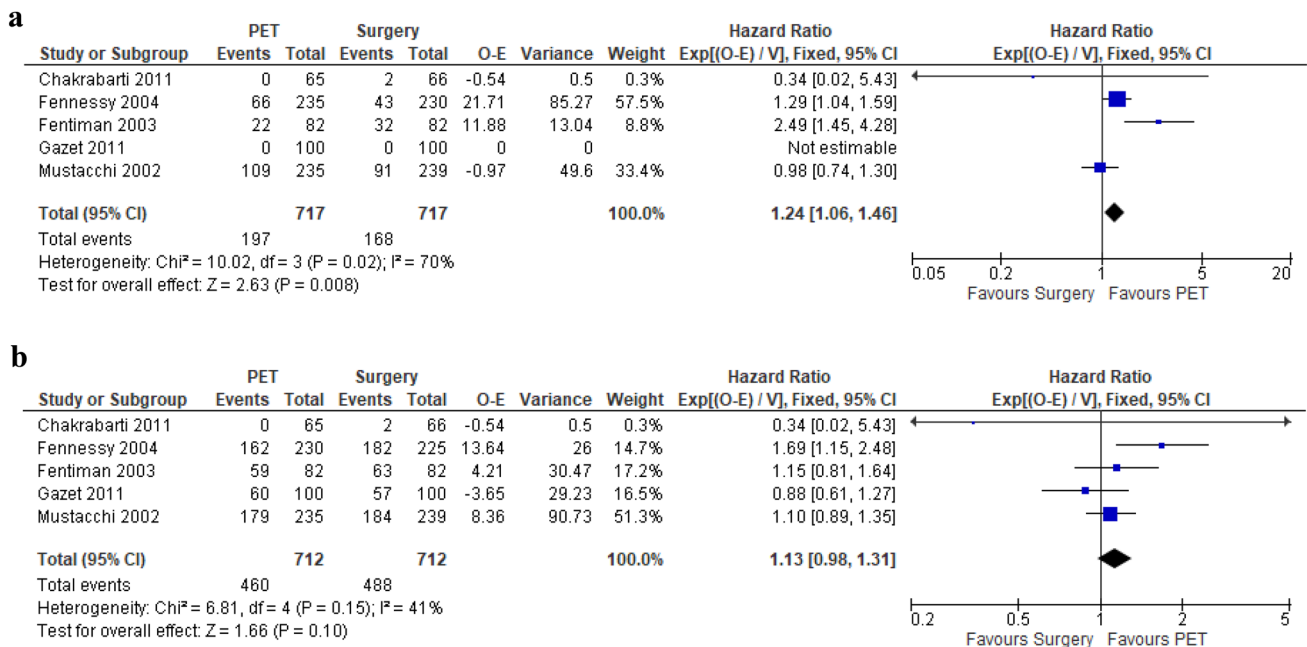


Fig. 4 Forest plots comparing PET and surgery: **a** overall survival rates. **b** Breast cancer-specific survival rates

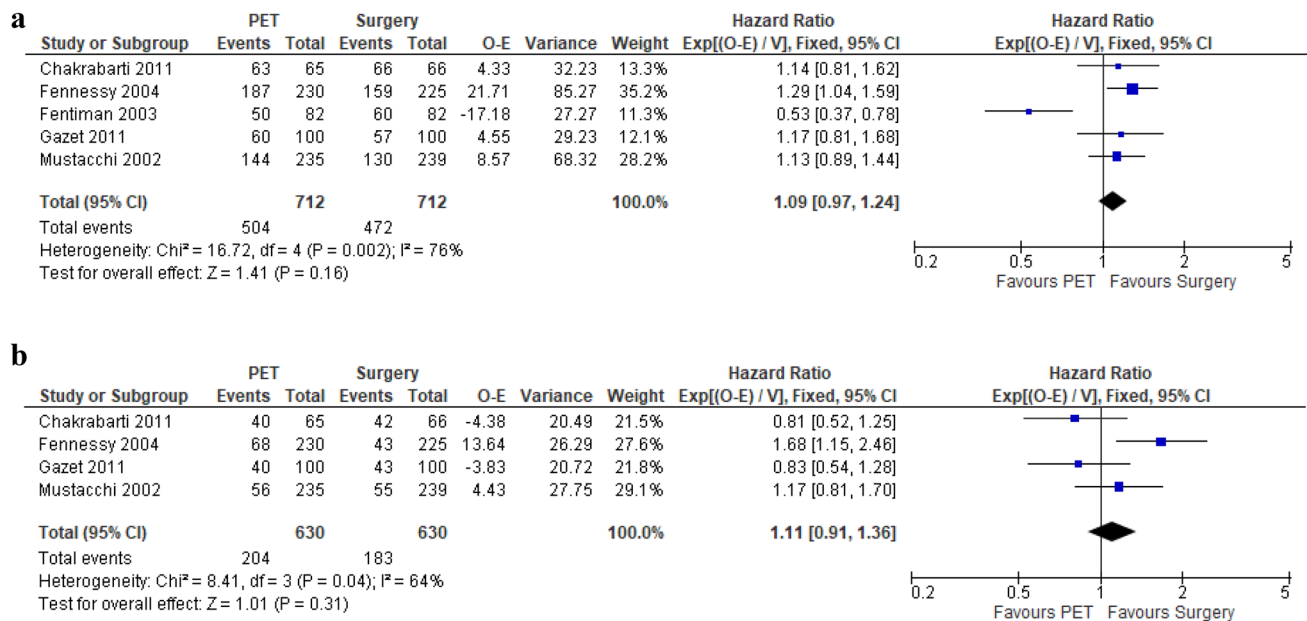


Fig. 5 Forest plots comparing PET and surgery: **a** all-cause mortality rates. **b** Cancer-specific mortality rates

treatment with PET alone, avoiding surgery, in terms of time to development of local recurrence is 1.1 years.

Has the SARS-CoV-2 pandemic lead the way to what may become the standard of care for early and noninvasive breast cancer? Possibly not, as our meta-analysis demonstrates. While the surgical profession is not known for its agility historically, this unprecedented pandemic brought leaders together on both local and national levels. Breast cancer

care was quickly modified without knowledge of impact on oncologic outcomes. New ways to care for patients included telehealth, and technology was offered by surgeons [1, 4]. Surgeons were pushed to make treatment decisions based on public health concerns rather than solely on the patient’s diagnosis. Virtual tumor boards were formed and there were increased numbers of regional webinars to discuss patient management in a broader sense. Though many clinical trials

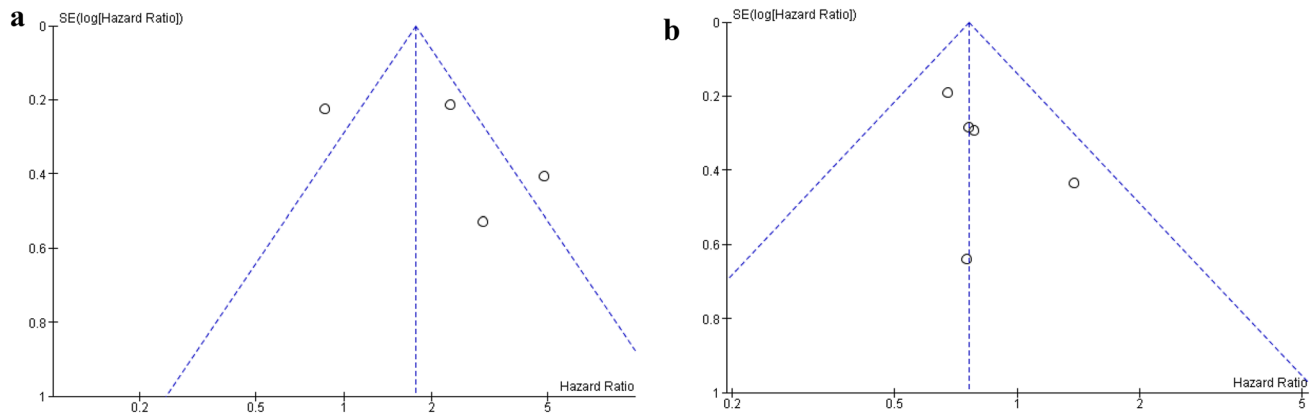


Fig. 6 Funnel plots of hazard ratio and standard error of log hazard ratio: **a** local recurrence (progression) rates. **b** Distant recurrence (progression) rates

were suspended, patients who already started investigational drugs were monitored remotely. Although, we cannot conclude omission of surgery altogether for otherwise operable breast cancer, there is a window of time that may be allotted to safely allow emergence from pandemic.

Limitations

This meta-analysis has several limitations. First, all studies only included women aged ≥ 70 years, making it difficult to extrapolate how younger patients may fare on solely PET. Additionally, the included studies did not stratify outcomes by tumor stage nor nodal status. Therefore, while we hypothesize that patients with less aggressive tumors may have more favorable outcomes on PET, this was not possible to prove. Similarly, the studies did not provide detailed information on treatment regimen in the PET arms of each trial when recurrence was identified. Further, how recurrence was defined was not known. This made it difficult to sum and compare outcomes of the PET arms of each study.

Conclusion

PET alone is inferior to surgery in the treatment of operable, early-stage invasive breast cancer. However, it may be acceptable to delay curative breast cancer surgery without risk of progression for 1.1 years or longer. Going forward, the National Cancer Database (NCDB) will further elucidate the long-term oncologic impact of the disruption of cancer care during the pandemic. Additional research is needed to assess the effectiveness and safety of the alteration of care. If nothing else, the pandemic demonstrated that it is possible for providers, payers, and patients to come together to facilitate change safely, and without progression of disease for at least a short time interval.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12282-021-01302-4>.

Author contributions All authors have contributed to the following: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Conflict of interest All authors declare they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Not applicable as this is a summary design study.

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