Title: The association between guideline adherence, age and overall survival among women with non-metastatic breast cancer: a systematic review

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Abstract

Introduction:

Conformity with treatment guidelines should benefit patients. Studies have reported variation in adherence to breast cancer (BC) guidelines, particularly among older women. This study investigated (i) whether adherence to treatment guideline recommendations for women with non-metastatic BC improves overall survival (OS), (ii) whether that relationship varies by age.

Methodology:

MEDLINE and EMBASE were systematically searched for studies on guideline adherence and OS in women with non-metastatic BC, published after January 2000, which examined recommendations on breast surgery, chemotherapy, radiotherapy or endocrine therapy. Study results were summarised using narrative synthesis.

Results:

Sixteen studies met the inclusion criteria. The recommendations for each treatment covered were similar, but studies differed in their definitions of adherence. 5-year OS rates among patients having compliant treatment ranged from 91.3%-93.2%, while rates among patients having non-compliant treatment ranged from 75.9%-83.4%. Six studies reported an adjusted hazard ratio (aHR) for non-compliant treatment compared with compliant treatment; all concluded OS was worse among patients whose overall treatment was non-compliant (aHR range: 1.52 [1.30-1.82] to 2.57 [1.96-3.37]), but adjustment for potential confounders was limited. Worse adherence among older women was reported in 12/16 studies, but they did not provide consistent evidence on whether OS was associated with treatment adherence and age.

Conclusions:

Individual studies reported that better adherence to guidelines improved OS among women with non-metastatic BC, but the evidence base has weaknesses including inconsistent definitions of adherence. More precise and consistent research designs, including the evaluation of barriers to adherence across the spectrum of healthcare practice, are required to fully understand guideline compliance, as well as the relationship between compliance and OS following a BC diagnosis.

Keywords: guideline adherence, breast cancer, overall survival

Introduction

Breast cancer (BC) is the leading global cause of cancer-related death for women, with just over 600,000 deaths in 2017[1]. In the UK, BC is the commonest form of female cancer, with just under 55,000 cases recorded each year[2], and is the second most common cause of cancer related death among women[3]. There is an abundance of high-quality evidence from randomised controlled trials to guide the treatment of breast cancer[4-6]. Nonetheless, studies have reported different breast cancer specific survival rates across Europe and America[7-9]. Understanding the underlying causes of this variation, and identifying ways to reduce it, remain a significant clinical priority[10],[11].

Clinical Practice Guidelines (CPGs) provide an evidence-based approach to the diagnosis and management of cancer. These CPGs have also informed the definition of clinical indicators, which enable the benchmarking of care across health care providers and support quality improvement[12]. An international comparison of breast cancer CPGs in 2012 reported that there were only marginal differences in treatment recommendations[13]. Nonetheless, there have been differences identified in the quality indicators used to evaluate the BC pathway by different countries[14]. Variation in patterns of breast cancer treatment have been widely reported[15-17], and it is possible that poor adherence to CPG recommendations contributes to worse survival rates among women with breast cancer.

Studies that documented variation in BC treatment have highlighted patient age as one of the main factors associated with non-compliance with guideline recommendations[18, 19],[20]. This could be because older age is associated with greater levels of comorbidity and frailty, which may preclude some patients from receiving standard treatment[21]. The underrepresentation of older patients in clinical trials may also contribute, as this can make clinicians less confident in using guideline recommendations for older individuals[22]. There may also exist an age-related bias in treatment selection by clinicians.

The aim of this systematic review was to evaluate the evidence that better adherence to treatment guidelines is associated with improved overall survival (OS) among women with non-metastatic (M0) BC. In addition, we investigated whether the reported relationships between overall survival and guideline adherence varied by age at diagnosis.

Methods

Study eligibility

The systematic review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist[23] (see Appendix A). Studies were eligible for inclusion if they assessed the relationship between OS and the degree of adherence to guidelines, quality indicators or standards for BC treatment. The review was limited to observational studies published between January 2000 and December 2020 to ensure the guidelines reflected contemporaneous BC management. 'Guideline adherence' was defined as compliance to either single or multiple recommendations from a clinical practice guideline on BC treatment, or related standard or quality indicator. For ease of reporting, 'guideline compliance' is used throughout the review to apply to these three elements.

BC treatment was defined to include breast surgery (BrS), axillary surgery (AS), radiotherapy (RT), chemotherapy (CT) or anti-estrogenic endocrine therapy (ET). Biological therapies, such as anti-HER2 treatment (trastuzumab), were not analysed as a standalone treatment. However, if they were included in a study in combination with other systemic or adjuvant treatments, the study was included in the review. The study population encompassed adult (>18 years) women with stage 0-3 BC. Studies which addressed guideline adherence among patients with metastatic BC only were not within scope. Publications were excluded if they: a) were written in a non-English language; b) analysed guideline adherence amongst a specific sub-group of patients unrelated to the aim of this study; c) did not include OS as an outcome; d) included only patients diagnosed prior to the year 2000; e) were described in conference abstracts only. In instances where multiple publications were identified as describing results from the same or related cohort of patients, the publication that provided the most information to answer the study questions was selected. Publications that used the same data source but analysed separate treatments were included.

Search strategy

Search terms were created to reflect three key concepts: adherence to guidelines, cohort of BC patients, and oncological outcomes. Search terms were trialled until a final strategy was agreed by the study authors (Appendix B, Table B.1 and B.2). A single author (KM) performed the electronic searches of two online database (EMBASE and MEDLINE) via the OVID platform in December 2020. The returned titles and abstracts were scanned, and potentially relevant articles were selected for full-text review. Citations in an earlier systematic review were also checked[24]. The final selection from the set of full-text articles was independently performed by two authors (KM and IK), with disagreements resolved in discussion with senior authors (DAC and MP). Publications excluded from this review after evaluation of the full-text are described in Appendix C.

Data extraction

Information on study characteristics was extracted by two authors (KM and IK) and included the article information (e.g. author, publication year), population demographics, study methodology, key findings, hazard ratios for overall compliance to treatment guidelines and for individual treatments, and 5-year OS rates stratified by adherence. When available, information on results stratified by age group was also extracted, as was reference to variables that might affect guideline compliance (e.g. social determinants of health and financial constraints).

Study quality assessment

The Newcastle Ottawa Scale[25] (NOS) was used to analyse the quality of each study. This appraisal tool contains nine items that cover three quality domains. Each study is assigned a score between 0 to 9, with a higher score indicating superior study quality. Two authors (KM and IK) independently assessed each paper, and discrepant scores were resolved by discussion.

Analysis of results

Studies were analysed using a narrative synthesis approach[26]. This method was selected due to the high degree of heterogeneity identified among the studies in terms of the patient population, treatments covered, definition of adherence, and BC guideline or standard analysed. This heterogeneity meant that meta-analysis was not appropriate.

All hazard ratios (HR) and their 95% confidence intervals (CIs) are presented for non-compliance to treatment guidelines (i.e. a HR >1 indicates improved OS among those whose treatment was compliant with guidelines). The extracted HRs were transformed to create the reciprocal if they were presented for compliance. If available, the HR for overall compliance to all treatments was extracted from each study and presented in a forest plot, drawn using STATA version 15.1.

Results

Included studies

The electronic database searches identified 5207 studies. The titles and abstracts of papers produced from this search were screened for relevant articles. Sixty-seven papers were selected for full-text review; 64 from the electronic databases and three were selected from the reference list of an earlier systematic review[24]. Of these, 16 papers met the study eligibility criteria[27-42]. The stages of the study selection are presented in Figure 1.

Study characteristics and quality assessment

Table 1 summarises the characteristics of the 16 publications. The papers had adopted three main study designs: population-based cohort studies which used cancer registry databases (N = 8)[31-35, 37, 38, 42], multi-centre cohort studies (N = 5)[27, 36, 39-41], or case series which used data from single institution databases (N = 3)[28-30]. Ten studies[27, 29, 31, 32, 35, 37-41] reviewed adherence to clinical guidelines, whilst six[28, 30, 33, 34, 36, 42] used quality indicators or standards. The range of different guidelines, clinical indicators or standards reflected the diverse range of healthcare systems covered (eight studies were conducted in Europe, five in the United States and three in East Asia). Nonetheless, the guideline recommendations were often similar.

Most studies included patients with stage 1-3 BC, with four studies[30, 31, 33, 41] also including patients with non-invasive disease (stage 0). Half of the studies (N = 8) enrolled patients according to their disease characteristics, while the other eight contained only those patients who had received primary breast surgery. Studies in the latter group were unable to examine questions about the receipt of surgery, although one considered the type of surgery received by patients (see Table 1). There was considerable diversity in the treatments covered across the two sets of eight studies, with only three studies covering all five treatments.

The quality of the studies was variable, with the total number of stars awarded according to the NOS criteria ranging from 2/9 to 9/9 (Appendix D). Most studies performed poorly in the NOS domain on outcomes, with ten scoring 0 or 1 star from a maximum of 3. Although the primary outcome was long-term survival, only four studies adequately reported how many patients were lost to follow-up.

Definition and rates of adherence to individual recommendations

Table 2 presents the definition of compliance for each treatment recommendation adopted across the studies, along with the percentage of patients who met each definition. There were a number of differences in the interpretation of compliance across the studies. First, the majority[27, 28, 31-33, 35, 36, 38, 39, 41, 42] (N = 11) defined compliance in relation to the omission of treatment, a reflection of the selected guideline recommendations. Three studies[34, 37, 40] considered recommendations that corresponded to over-treatment (e.g. receipt of treatment when not recommended or receiving a more invasive therapy).

The reported levels of compliance for the complete cohort of eligible patients were generally high, exceeding 80% in many studies for each of the five therapies (Table 2). Adherence to recommendations on endocrine therapy was broadly comparable across studies, and ranged from 85% to 96%[28, 31, 33, 34, 40, 41]. For the other treatments, the differences in the definitions of

compliance prevented a meaningful comparison of adherence rates across the studies. In addition, the recommendations could differ in their specificity. For example, six studies reported levels of adherence with RT after breast-conserving surgery (BCS), with rates ranging from 79% to 97%[28, 33-35, 39, 41], while four studies reviewed receipt of adjuvant RT without categorisation by type of surgery, with rates of adherence ranging from 84% to 93%[27, 31, 37, 40].

Other sources of difference included: (i) studies reviewing compliance in relation to all systemic or adjuvant treatment recommendations, and therefore the rates of adherence for individual therapies were not presented[27, 32], and (ii) studies only reporting rates of compliance according to a factor (such as patient age and disease stage)[37, 38, 42].

Few studies reported on whether guideline adherence was related to other determinants such as patient ethnicity, level of education, employment status, socio-economic status, and financial arrangements[27, 31, 32, 35, 42]. The most comprehensive analysis was performed by Andreano et al., who found small but statistically significant differences in compliance by patient education (p=0.025), employment (p=0.007), marital status (p=<0.001) but not by deprivation index (p=0.556) [27]. Guideline adherence was reported to be influenced by ethnicity by two studies from the USA[35, 42] and the study from Singapore[31].

The association between guideline adherence and overall survival

Table 3 summarises information on the relationship between the overall percentage of patients receiving guideline compliant treatment and 5-year OS rates. In calculating overall compliance, most studies defined this as receiving treatment that was compliant with all recommendations / indicators covered by the study and applicable to the patient given their disease characteristics (one study placed the cut off at ≥ 80% of their seven indicators[27]). Of the 13 studies which assessed more than one treatment modality, five reported the percentage of patients who received overall compliant treatment, with values ranging from 52% to 79%[27, 28, 32, 34, 40]. Yun et al.[41] reported overall adherence rates by year (1993 21% vs. 2002 84%) and Van de Water et al.[37] gave results for two age groups (<65yrs: 62% vs. ≥75yrs: 56%) respectively.

Five studies reported rates of 5-year OS for adherent and non-adherent patient groups. Across these studies, the 5-year OS rates for patients who received adherent treatment were very similar (range 91.3% - 93.2%) despite the differences in the definition of compliance. The 5-year OS rates for patients who were classified as receiving non-adherent treatment were uniformly lower than the rates for

compliant patients, and ranged from 75.9% to 83.4%[27, 34, 36, 39, 40]. Other studies reported 5-year survival rates by different patient subgroups (tumour type) or type of treatment.

Six studies used a multivariable model to derive adjusted hazard ratios for the relationship between overall compliance and OS[27, 28, 34, 36, 39, 40] for the overall cohort. Each reported that adherence to treatment guidelines was associated with improved survival (Figure 2). Adjustment for patient characteristics attenuated the effect size, with the largest HR being reported by Wockel et al. (5-yr OS adherent vs non-adherent: 92.4% vs 76%; adjusted HR 2.57, 95% CI 1.96 – 3.37).

A number of studies used multivariable models to examine OS and treatment compliance by treatment modality. Vogsen et al. found adherence to ET guidelines was not associated with improved survival[38], and Yun et al. reported adherence to RT or CT guidelines did not significantly affect survival outcomes[41]. In contrast, Wimmer et al. reported that adherence to adjuvant RT guidelines was associated with better survival[39]. Kantor et al. found no difference in OS between US census regions with high compliance rates, compared with regions with low compliance for RT, CT or ET[33]. Among the sixteen studies, we reviewed whether patient, social and financial factors had been included as covariates in the multivariable survival analyses. Seven studies included a measure of co-morbidity (five of which used the Charlson index[27, 32-34, 42]), five included patient ethnicity[31-33, 35, 42], and three studies adjusted for socio-economic status[27, 32, 33]. Two studies adjusted for patient insurance status[32, 33]. Therefore, the majority of papers did not account for various predictors known to be associated with adherence and survival within their analysis.

Association between guideline adherence, overall survival and patient age

Patient age at diagnosis featured in different parts of the study design across the reviewed studies. First, some studies restricted the definition of recommendation compliance to specific age groups. Eight studies adopted this approach in relation to recommendations for CT[27-33, 37] and two studies did this in relation to recommendations for adjuvant RT after BCS[30, 33]. In each case, the cohort was restricted to younger patients, typically, those patients aged under 70 years.

Second, age featured in the reporting of what proportion of patients received guideline compliant care (i.e., when judged across all applicable therapies). Of the 13 studies that did this[27-29, 31, 32, 34-40, 42], 12 reported lower rates of guideline adherence to one or more treatments among older patients[27, 29, 31, 32, 34-40, 42]. There were some exceptions to this finding, with varied adherence reported by age to ET[31, 37, 38] or surgery[31]. Wockel et al. found that the percentage of patients receiving guideline adherent treatment reduced as age increased, but patients aged under 35 years

also had lower than average rates of compliance[40]. One study showed a positive correlation between adherence and age[28]. In a study that included age in the definition of compliance with CT[29], age was reported as the dominant reason for the deviation from guideline recommendations.

Some studies included age at diagnosis in the analysis of the relationship between guideline compliant treatment and OS. In eight studies, age was simply used for case-mix adjustment[32-35, 39-42]. However, four studies explored whether the relationship between guideline compliant treatment and OS was affected by patient age, typically by splitting the cohort into groups[27, 28, 31, 36]. This produced separate estimates of the HR for non-compliant care by age, but it did not allow for the difference between the two HR to be statistically tested. For example, Ho et al. split their cohort into two age groups (<70 or ≥70) and reported improved OS for patients receiving compliant treatment (BrS, CT, RT and ET). However, the survival benefit was larger in the younger age group than the older age group (e.g. breast surgery: <70 yrs HR 2.20 [95% CI 1.80 – 2.83]; ≥70 yrs HR 1.74 [95% CI 1.33 – 2.29]) but the study did not determine if the difference was statistically significant[31]. Only Vogsen et al. formally tested the statistical significance of an interaction between age and compliance, and found that compliance with surgery guidelines was associated with a significantly improved survival in younger patients (≤80 yrs HR 8.38 [95% CI 4.46 – 15.8]), and this effect was larger than in the over 80 age group (HR 2.56 [95% CI 1.63 – 4.01])[38]. Finally, Van de Water et al. found improved OS with adherent treatment using Cox regression analysis for patients in two distinct age groups (less than 65, and 75 and over), but observed no association when using instrumental variable analysis (a technique devised to reduce the effect of unmeasured confounders)[37].

Discussion

Main findings

This study examined the evidence on variation in rates of guideline adherence and whether adherence to treatment guidelines was associated with OS among patients with non-metastatic BC. Across the 16 papers identified, reported rates of guideline adherence were generally high for all treatment types. This is an encouraging result for the breast cancer community and patients. There was also consistency among studies in finding that adherence to guideline recommendations is associated with improved OS. Since guidelines in BC generally draw on an extensive set of results from clinical trials, adherence might be expected to have a positive influence on subsequent survival outcomes. Nonetheless, the trials are typically limited to comparing individual treatments and the value of the reviewed studies was their focus on compliance across multiple therapies.

The interpretation of these results is not straightforward. The studies differed in many aspects of their design, including: the patient cohorts, the treatments covered, the definition of adherence and the method of analysis. All studies used observational designs and while a few studies[35, 37] attempted to use statistical techniques advocated for estimating causal relationships, most relied on Cox regression models and incorporated a limited number of potential confounders. These factors were typically limited to age and breast cancer characteristics. Only a minority included a measure of comorbidity and other potential confounders introducing some risk of bias. The lack of information on levels of adherence in relation to social and financial factors was also noted. As the studies in this review were conducted in European, US or city-state Asian countries, it is possible that resource constraints were not considered to be strongly associated with non-standard treatment. However, the influence of resource availability and financial barriers for patients are likely to vary between settings, particularly in low and middle-income countries where breast cancer guidelines may not be adapted to meet the characteristics of their health care systems[43].

The review also examined the strength of evidence on potential impact of age at diagnosis on the association between OS and treatment adherence. Six of the sixteen studies considered this question directly, with twelve of the sixteen studies reporting that the proportion of patients with compliant care was lower among older patients. Among these studies, the results were inconsistent, and the quality of the evidence was generally poor. The typical analytical approach was to estimate adjusted HRs using separate models for each age group, and only one study[38] tested the differences in the HRs for each age group for statistical significance.

Two previous systematic reviews have evaluated guideline compliance among patients with BC[20, 24]. Our review found the median level of adherence across all treatment modalities was 69%, which is higher than that reported by Niño de Guzmán et al. (57.5%)[20]. Our study provides a more contemporaneous view on adherence to CPGs, since we excluded studies where the patient cohort were only diagnosed prior to the year 2000, which was not applied by the authors of the previous review. In a meta-analysis of four studies on breast cancer patients, Ricci-Cabello et al. estimated that guideline adherence was associated with a 33% reduction in mortality, but the included studies were wide ranging in their scope, and analysed a different number of recommendations for a variety of diagnostic processes and/or treatment modalities. Both of these systematic reviews only included publications from European or European Union countries, thereby restricting the extrapolation of their results on a global scale.

Guideline adherence among older patients with breast cancer

Increasing age is known to be associated with deviation from standard treatment practices[44, 45] and it was not surprising to find that 12 of the 16 studies reported an association between older age and non-adherence to treatment guidelines. This finding was also reported by Niño de Guzmán et al. Our review found that, among the 60 guideline recommendations examined, 10 included chronological age as a criterion within treatment recommendations. Eight related to chemotherapy, where the adverse impact among unfit older patients is recognised[46, 47]. Nonetheless, among appropriately selected older individuals with certain tumour subtypes, such treatment can provide some survival benefit[47, 48]. A recent qualitative study of 30 women aged 70 or over found approximately half agreed with cancer guidelines which were age-based[49]. Women who were opposed to age-based guidelines cited that factors such as overall health status and estimated life expectancy should be used instead to inform treatment decisions.

A challenge for studies evaluating the association between survival and guideline adherence is understanding the degree to which deviations from guideline recommendations are justifiable because of contraindications and patient preferences[50]. To understand if deviations from standard practices reflect appropriate modifications rather than under treatment requires data on treatment planning and decision making, and this highlights an important role for observational studies with bespoke prospective data collections. Data on treatment decisions are typically unavailable in the large national datasets used in retrospective observational studies.

Some studies[31, 38] in this review showed improved survival among the older population with adherent treatment, but the benefit was often less when compared with younger women, and due to inconsistencies in how studies approached survival by age group, we are unable to present a more comprehensive picture. Increased prevalence of comorbidity and frailty among older BC patients can adversely affect survival outcomes[51], and therefore accounting for these competing mortality risks within survival analysis is important to minimise confounding. However, our review found that only seven of the 16 studies adjusted for comorbidity.

Strengths and limitations

There are strengths to this review. It included an international selection of publications, and examined how guideline adherence and survival might be influenced by patient age[16]. This review also has some limitations. Our search strategy was restricted to publications in the English language held in two electronic databases, and a single author performed the initial screen of search results, which may have resulted in potentially relevant studies being excluded. Our study focused on a single

outcome (overall survival), which meant we were unable to comment on other important outcomes, such as recurrence free survival or quality of life.

Implications for clinical practice and research

This study has important implications for health care professionals and organisations who design and use CPGs. CPGs and quality indicators appear to have a positive impact on improving OS, and this should encourage clinicians to reflect locally on the dissemination, uptake and the reduction of barriers to implementation of national guidance. During the implementation process, training and educational resources for clinical teams on how to apply CPGs within their practice can improve adherence rates[52, 53]. The ability to perform local audit of quality standards has been facilitated in the UK by initiatives such as the Clinical Outcomes Publication and the National Clinical Audit and Patient Outcomes Programme[54]. As part of these programmes, NHS organisations are able to review their own data for specified quality indicators, and compare their performance at a regional or national level.

The evidence analysed in this review has various methodological limitations, which has important implications for those conducting research on the association between guideline adherence and outcomes. First, there was heterogeneity in the study designs, cohort selection, definition of adherence and the presentation of results. It is likely that some of the variation across the studies in the reported rates of adherent treatment stems from these methodological differences. Future research would benefit from using a standardised and rigorous approach to the definition of over and under treatment, which have been proposed in a recent literature review[55]. In addition, a definition of compliance based on the summed effect of both over and under treatment should be avoided, since the two definitions are distinct and combining them does not allow the (often complex) effect on outcomes to be analysed.

Second, the reporting and analysis of survival rates also varied. Some authors stratified results by treatment or other variables, which limited our ability to discern an OS effect for guideline adherence treatment. The reliance on observational studies means that the results are prone to bias, notably due to confounding by indication. We cannot therefore make a causal assumption about the observed relationship between adherence and survival.

Conclusions

This systematic review of evidence on the association between adherence to treatment guidelines and OS among patients with M0 BC has shown that most studies reported compliance with treatment

guidelines was associated with improved OS. Nonetheless, the quality of the studies varied and more standardised approaches are required to increase confidence in those conclusions. The finding that older age at diagnosis was associated with worse levels of adherence should encourage guideline developers to emphasise the importance of including the assessment of overall patient fitness in informing recommendations, rather than chronological age alone, to prevent the exclusion of fit older patients from receiving standard treatment. The development of treatment guidelines requires considerable resources and at present the influence of guideline adherence on survival among older patients with BC is unclear. Further research is required to understand the reasoning behind guideline deviation among this population.

Supporting information

This systematic review was not registered with an online database. A review protocol was prepared for internal use by the study authors and has not been published. Data and other material used for this review is not publicly available.

Funding

This study was undertaken as part of the work by the National Audit of Breast Cancer in Older Patients (NABCOP), which aims to evaluate the care of older women with breast cancer in England and Wales (www.nabcop.org.uk). The Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-programmes). Neither HQIP nor the funders had any involvement in the study design, analysis, interpretation of findings, writing of the report, or in the decision to submit the article for publication.

Conflict of interest

K. Clements declares funding for a Breast Cancer Research Manager role within the Screening Quality Assurance Service at NHS England and NHS Improvement. The remaining authors declare no conflict of interest.

Abbreviations:

aOR: adjusted odds ratio
AI: aromatase inhibitor
ALND: axillary lymph node dissection
AS: axillary surgery
BC: breast cancer
BCS: breast conserving surgery
BrS: Breast surgery

CI: confidence interval
CPGs: clinical practice guidelines
CT: chemotherapy
DCIS: ductal carcinoma in situ
EBC: early breast cancer
ER: estrogen receptor
ET: endocrine therapy
GnRH: gonadotropin releasing hormone
HER2: human epidermal growth factor receptor 2
HR: hazard ratio
IBC: invasive breast cancer
LABC: locally advanced breast cancer
LCIS: lobular carcinoma in situ
LN: lymph node
Mx: mastectomy
NACT: neoadjuvant chemotherapy
NOS: Newcastle Ottawa Scale
N/A: not applicable
NCCN: National Comprehensive Cancer Network
NR: not reported
OS: overall survival
PMRT: post-mastectomy radiotherapy
PT(s): patient(s)
RT: radiotherapy
SLNB: sentinel lymph node biopsy
T-mab: trastuzumab

Tables and figures

Figure 1. Flow chart of search strategy and study selection process.

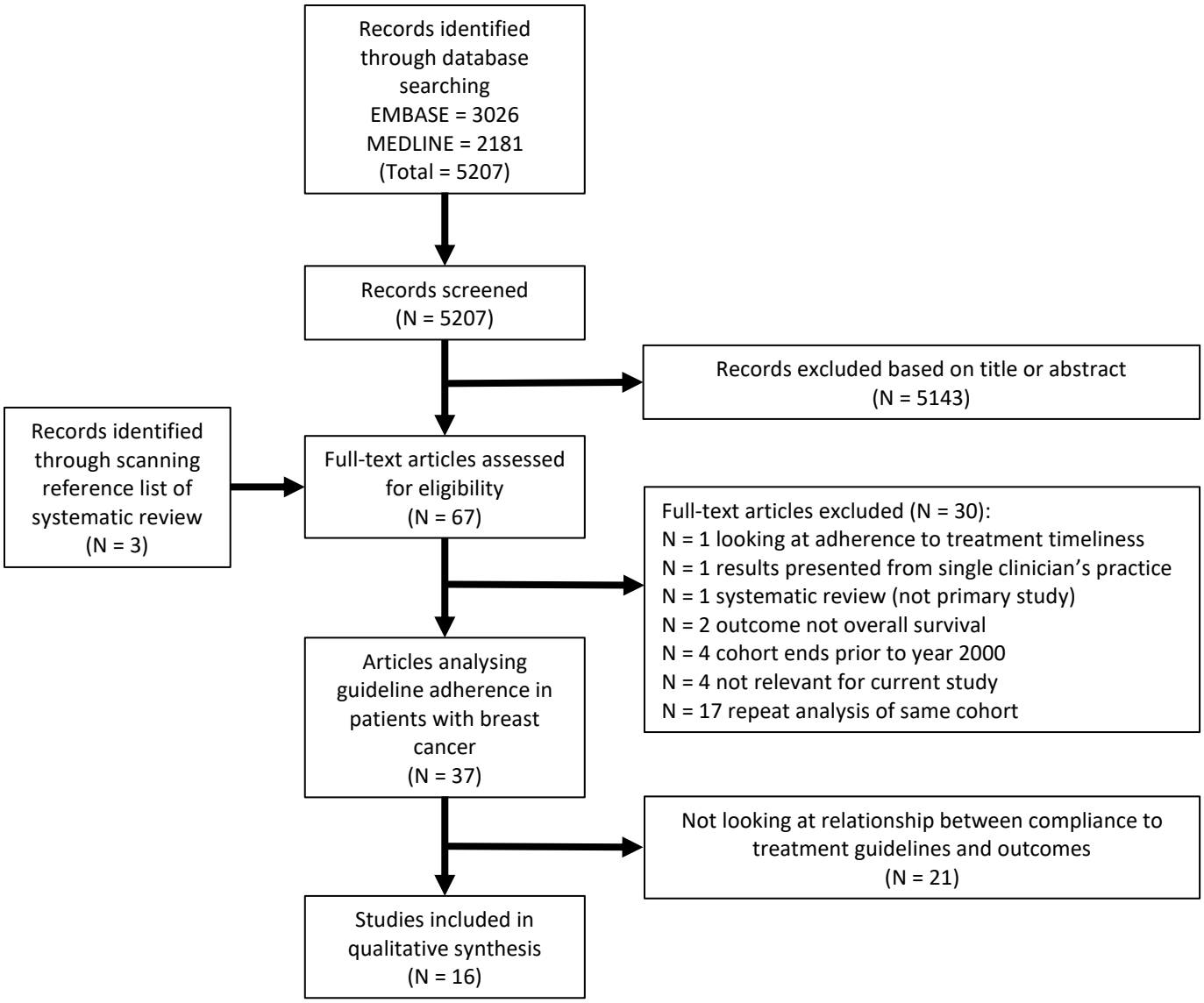

Figure 2. A forest plot displaying the hazard ratios for the effect of non-adherence to all treatment guidelines.

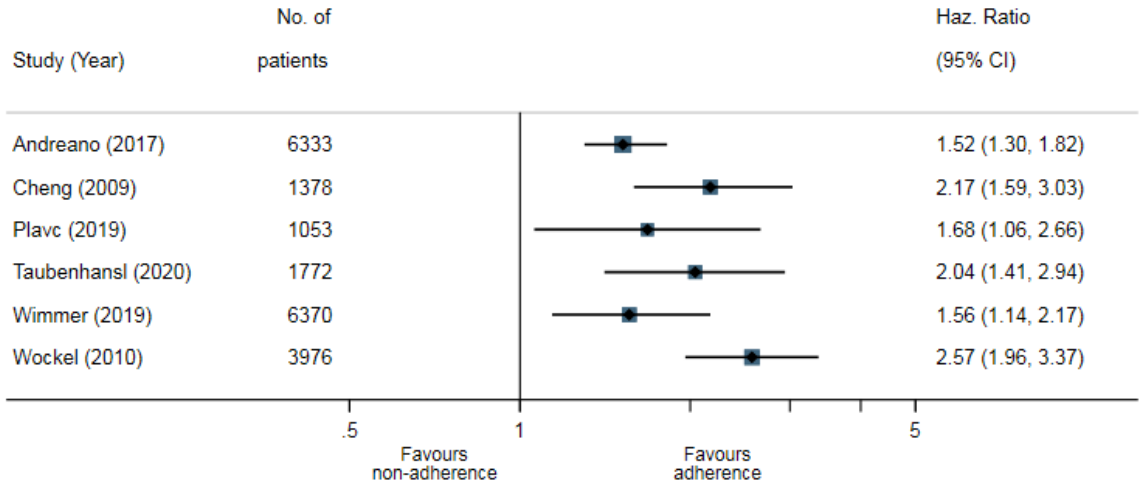

Table 1. Key characteristics of studies selected for the systematic review (N = 16).

Author (Year)	Study time period	Country	Cohort design	Data source	Patient cohort	Additional inclusion criteria	Level of adherence compared across	Guideline or standard	Treatments analysed					Outcome(s)
									BrS	AS	CT	RT	ET	
Studies with enrolment criteria based on diagnosis														
Cheng (2009)	1995-2001	Taiwan	Case series	Single hospital cancer database	Stage 1-3	-	-	National quality indicators (2000/01)		X	X	X	X	OS, PFS
Dooley (2011)	2001-2008	USA	Case series	Single hospital cancer database	Stage 0-4	-	-	Center for Medicare and Medicaid Services quality standards (2007)			X	X	X	OS, DFS
Ho (2020)	2005-2015	Singapore	Population	Six hospital cancer databases	Stage 0-3	-	-	NCCN (2018) and St. Gallen international consensus guidelines (2005).	X		X	X	X	OS
Kantor (2018)	2014-2015	USA	Population	NCDB	Stage 0-3	-	9 USA census regions	CoC quality metrics (2006, 2014)	X		X	X	X	OS
Plavc (2019)	2013	Slovenia	Population	National Slovenian cancer registry	Stage 1-3	-	-	EUSOMA quality indicators (2010)	X	X	X	X	X	OS, EFS
Taubenhansl (2020)	2003-2015	Germany	Multi-centre	Regional cancer registry	[Tany,N1-3,M0], HR positive	Received ET	-	German Cancer Society quality indicator (2019)			X			OS, DFS
Van de Water (2012)	2005-2008	The Netherlands	Population	National cancer registry database	T0–T2,N0–N1,M0	<65 yrs; ≥75 yrs	Age groups	Dutch national guidelines (2005, 2006, 2008)	X	X	X	X	X	OS, RS
Vogsen (2020)	2008-2012	Denmark	Population	DBCG database	EBC	Aged ≥70 yrs	-	Danish national guidelines	X	X	X	X	X	OS
Studies with enrolment criteria based on patients undergoing surgery														
Andreano (2017)	2007-2012	Italy	Multi-centre	Regional cancer registry	Stage 1-3, surgery	-	-	NICE (2009) and ESMO (2015)		X	X	X	X	OS
Chereau (2011)	2003-2005	France	Case series	Single hospital cancer database	IBC, surgery	-	-	Local guideline			X			OS, DFS
Hsieh (2019)	2011	USA	Population	Regional cancer registry	Stage 1-3, surgery, RT	-	Tumour sub-type	NCCN (2019)			X		X	OS, BCSS
Sun (2015)	1997-2010	USA	Population	Eighteen SEER registries	Stage 1, BCS	Aged ≥55 yrs	-	NCCN senior adult oncology (2014)		X		X		OS, BCSS
Wimmer (2019)	2003-2013	Germany	Multi-centre	Regional cancer registry	Stage 1-3, BCS	-	-	Step 3 German Cancer Society guidelines (2017)				X		OS, RFS
Wockel (2010)	2001-2005	Germany	Multi-centre	Single university hospital and multiple affiliated hospital databases (BRENDA study)	Stage 1-3, surgery	Positive resection margin	-	Step 3 German Cancer Society guidelines (2004); St Gallen international consensus guideline (2004)	*	X	X	X	X	OS, RFS
Yun (2007)	1993-2002	Korea	Multi-centre	Four hospital cancer databases	Stage 0-3, surgery	-	-	NIH guideline (2001) and St. Gallen international consensus guidelines (1998)			X	X	X	OS
Zhao (2019)	2004-2015	USA	Population	NCDB	[T1N0, T2/3N0, TanyN2/3], surgery	For T1N0 : aged <70 yrs	Tumour sub-type	OSCS (2015)		X	X	X	X	OS

Abbreviations: **AS:** axillary surgery; **BCS:** breast conserving surgery; **BCSS:** breast cancer specific survival; **BRENDA:** Breast Cancer Care Under Evidence-based Guidelines; **BrS:** breast surgery; **CoC:** Commission on Cancer; **CT:** chemotherapy; **DBCG:** Danish Breast Cancer Cooperative Group; **DFS:** disease free survival **EBC:** early breast cancer; **EFS:** event free survival; **ET:** endocrine therapy; **ESMO**: European Society for Medical Oncology; **EUSOMA:** European Society of Breast Cancer Specialists; **HR:** hormone receptor; **IBC:** invasive breast cancer; **NCCN:** National Comprehensive Cancer Network; **NCDB:** National Cancer Data Base; **NICE:** National Institute for Health and Care Excellence; **NIH:** National Institutes of Health; **OS:** overall survival; **OSCS:** Operative Standards for Cancer Surgery; **PFS:** progression free survival; **RFS:** recurrence free survival; **RS:** relative survival; **RT:** radiotherapy; **SEER:** Surveillance, Epidemiology, and End Results Program.
*Adherence to breast surgery guidelines were assessed as type of surgery received, rather than received surgery versus not received.

Table 2. A comparison of definitions for guideline compliant treatment, as well as the percentage of patients' adherent to each recommendation.

Study	Definitions of non-compliance	Breast surgery		Axillary surgery		Radiotherapy		Chemotherapy		Endocrine therapy	
		Definition	% adherence	Definition	% adherence	Definition	% adherence	Definition	% adherence	Definition	% adherence
Studies with enrolment criteria based on diagnosis											
Cheng	Did not have recommended treatment	-		PTs with stage 1-3 BC had ≥10 LNs examined	97%	(1) Post-BCS within 6 weeks of BCS or CT if CT received (2) Post-BCS RT completed in 7 weeks (3) PMRT completed in 6 weeks	(1) 88% (2) 92% (3) 93%	**PTs aged <50 yrs with LN+**	97%	PTs with stage 1-3 ER +ve	88%
Dooley	Did not complete indicated treatment	-		-		**Post-BCS ≤1yr from diagnosis for PTs aged <70yrs**	NR	**Give ≤4 months from diagnosis in PTs aged <70yrs with stage 1-3, ER/PR-ve BC**	NR	Give ≤1 yr from diagnosis in PTs with stage 1-3 ER/PR +ve BC	NR
Ho	Did not have any treatment	All PTs with M0 BC	92%	-		LN+; post-BCS; tumour size >50mm or attached to chest wall	92%	**LN+; tumour size >20mm or attached to chest wall; tumour size >5mm & (G3 or ER-ve or HER2 +ve or age ≤35 years)**	82%	ER +ve or PR +ve	92%
Kantor	Did not have recommended treatment	BCS for PTs with stage 0-2 BC who had surgery	70%	-		**(1) Post-BCS ≤1yr from diagnosis for PTs aged <70yrs** (2) PMRT ≤1yr from diagnosis for PTs with ≥4 LN+	(1) 85% (2) 78%	**Give ≤120 days from diagnosis in PTs aged <70 yrs with T1cN0M0 or stage 1b-3, ER/PR-ve**	89%	Give ≤1 yr from diagnosis in PTs with T1cN0M0 / stage 1b-3, ER/PR+ve,	91%
Plavc	Undertreatment and overtreatment	BCS for PTs with tumour size <30mm	68%	(1) Receipt of SLNB for IBC (2) No ALND for pN0	(1) 89% (2) 94%	(1) Post-BCS (2) PMRT for ≥pN2a	(1) 92% (2) 90%	(1) ER-ve (tumour size >1cm/N+) (2) ER-ve inflammatory/LABC receiving NAC	(1) 83% (2) 83%	(1) Give for PTs with ER +ve BC (2) Do not give for PTs with ER -ve BC	(1) 96% (2) 100%
Taubenhansl	Did not have any treatment	-		-		-		PTs with Stage 1-3 ER/PR+ve and LN+	87%	-	
Van de Water	Undertreatment and overtreatment	All PTs with early stage BC	<65yrs: 100% ≥75yrs: 79%	All PTs with early stage BC	<65yrs: 98% ≥75yrs: 74%	Post-BCS; PMRT in case of non-radical resection / involvement of chest wall / axillary apex +ve	<65yrs: 93% ≥75yrs: 93%	**PTs aged <35 yrs; PTs aged <70 yrs with LN+; LN-ve and high risk characteristics**	<65yrs: 74% ≥75yrs: 100%	ER / PR +ve	<65yrs: 81% ≥75yrs: 79%
Vogsen	Did not have recommended treatment	All PTs had BCS or Mx (with SLNB or ALND if LN+)	70-74yrs: 95% 75-79yrs: 94% 80-84yrs: 84% ≥85yrs: 41%	-		NS	70-74yrs: 82% 75-79yrs: 65% 80-84yrs: 42% ≥85yrs: 22%	NS	70-74yrs: 70% 75-79yrs: 22% 80-84yrs: 0% ≥85yrs: 0%	NS	70-74yrs: 94% 75-79yrs: 80% 80-84yrs: 88% ≥85yrs: 77%

Study	Definitions of non-compliance	Breast surgery		Axillary surgery		Radiotherapy		Chemotherapy		Endocrine therapy	
		Definition	% adherence	Definition	% adherence	Definition	% adherence	Definition	% adherence	Definition	% adherence
Studies with enrolment criteria based on patients undergoing surgery											
Andreano	Proportion of met indicators <80%	No reoperation within 3m following BCS	97%	LN staging within 3m before surgery, or at surgery	85%	Post-BCS RT / RT for PTs with T3+ who received NACT and any primary surgery	84%	**Receipt of adjuvant treatment (defined as CT +/- ET [<70yrs]; CT or ET [>70yrs] for stage 2/3)**	76%	See CT column	See CT column
Chereau	PTs divided into 4 groups based on receipt of CT and indication	-		-		-		**Tumours >2cm / G3 / ER-ve / LN+ / PT <35yrs / G2 and Ki67 >25%**	64%	-	
Hsieh	Did not have recommended treatment	-		-		-		**Reported as % for systemic therapy (defined as receipt of CT, ET and T-mab based on histology)**	79%	See CT column	See CT column
Sun	Did not have recommended treatment	-		LN sampling among PTs with EBC who had BCS	85%	Post-BCS	79%	-		-	
Wimmer	Did not have recommended treatment	-		-		Post-BCS	97%	-		-	
Wockel	Undertreatment and overtreatment	(1) BCS in DCIS or LCIS <4 cm/R0; (2) Mx for malignant microcalcs / tumour >4cm / multicentric / inflammatory BC	(1) 85% (2) 85%	Level 1 and 2 dissection in IBC and removal of ≥10 LNs	87%	Post-BCS; PMRT in R1-R2 / LN+ ≥ 4 / T3-4	84%	NS	71%	ER +ve IBC (GnRH + tamoxifen in pre-menopausal PTs; tamoxifen or AI in post-menopausal PTs; post-CT), tamoxifen in DCIS	85%
Yun	Did not have recommended treatment	-		-		(1) Post-BCS (2) PMRT in ≥4 LN+ or tumour size ≥5cm	(1) 84% (2) 60%	Intermediate or high risk	84%	ER / PR +ve	86%
Zhao	Did not have recommended treatment	Negative resection margin	T1: 97% T2-3: 95% N2-3: 91%	(1) T1/T2-3: removal ≥2 LN (2) N2-3: removal ≥10 LN	T1: 74% T2-3: 78% N2-3: 78%	Definition: Any adjuvant treatment, defined as CT, RT, ET T1: 93% T2-3: 91% N2-3: 91%					

Abbreviations: **AI:** aromatase inhibitor; **ALND**: axillary lymph node dissection; **BC**: breast cancer; **BCS:** breast conserving surgery; **CT**: chemotherapy; **DCIS**: ductal carcinoma in situ; **EBC**: early breast cancer; **ER**: estrogen receptor; **ET**: endocrine therapy; **G?**: tumour grade; **GnRH:** gonadotropin releasing hormone; **HER2:** human epidermal growth factor receptor 2; **IBC:** invasive breast cancer; **LABC**: locally advanced breast cancer; **LCIS**: lobular carcinoma in situ; **LN**: lymph node; **?m**: months; **M0:** non-metastatic breast cancer; **Mx**: mastectomy; **NACT**; neoadjuvant chemotherapy; **NR**: not reported; **NS**: not stated within paper; **PMRT**: post-mastectomy radiotherapy; **PR**: progesterone receptor; **PT(s)**: patient(s); **RT**: radiotherapy; **SLNB**: sentinel lymph node biopsy; **T-mab**: trastuzumab.
Notes: If the study authors did not describe the guideline recommendation(s) being assessed for adherence within the paper, such as only containing a reference to the guideline, this is noted within the table as 'NS' for 'not stated'. Recommendations highlighted in grey include patient age within the criteria for adherence.

Table 3. Key results on the association between guideline compliant treatment and overall survival.

Study	No. of patients	Treatments analysed	Definition of compliance to all treatments	Percentage of patients with compliance to all treatments	Median follow-up (years)	5-year OS rate (%)		Adjusted HR[1] (95% CI) for non-compliance vs compliance
						Compliant	Non-compliant	
Studies with enrolment criteria based on diagnosis								
Cheng	1378	AS, RT, CT, ET	100% adherence to 10 indicators	74%	6.7	NR	NR	2.17 (1.59 - 3.03)
Dooley	1220	RT, CT, ET	NR	NR	3.7 (mean)	Reported by treatment		NR
Ho	19,241	BrS, RT, CT, ET	NR	NR	NR	Reported by (1) treatment; (2) treatment and age		NR
Kantor	305,391	BrS, RT, CT, ET	NR	NR	5.4	Reported by treatment		NR
Plavc	1053	BrS, AS, RT, CT, ET	100% adherence to 13 indicators	60%	4.5	93.2	75.9	1.68 (1.06 - 2.66)
Taubenhansl	1772	CT	N/A	N/A	6.4	91.3	76.8	2.04 (1.41 - 2.94)
Van de Water	31,520	BrS, AS, RT, CT, ET	100% adherence to guideline	<65yrs = 62% ≥75yrs = 56%	2.8	<65yrs = 94.7 ≥75yrs = 71.4	<65yrs = 92.1 ≥75yrs = 48.4	<65yrs = 1.75 (1.50 - 2.05) ≥75yrs = 1.62 (1.41 - 1.85)
Vogsen	441	BrS, AS, RT, CT, ET	NR	NR	Until June 2017	NR	NR	NR
Studies with enrolment criteria based on patients undergoing surgery								
Andreano	6333	AS, RT, CT, ET	≥ 80% adherence to 7 indicators	69%	5.6	93.2	83.4	1.52 (1.30 - 1.82)
Chereau	581	CT	N/A	N/A	4.0	*No CT, no indication: 99 CT and indication: 92	*CT and no indication: 95 No CT but indication: 95	NR
Hsieh	2214	CT, ET	100% adherence to guideline	79%	6.3	Reported by tumour subtype		NR
Sun	53,619	AS, RT	NR	NR	NR	Reported by treatment (10-yr OS)		NR
Wimmer	6370	RT	N/A	N/A	6.1	93.1	79.0	1.56 (1.14 - 2.17)
Wockel	3976	BrS, AS, RT, CT, ET	100% adherence to guideline	52%	NR	92.4	76.0	2.57 (1.96 - 3.37)
Yun	8407	RT, CT, ET	100% adherence to guideline	1993: 21% 2002: 84%	5.1 (mean)	NR	NR	NR
Zhao	833,748	AS, RT, CT, ET	NR	NR	NR	Reported by tumour subtype		NR

Abbreviations: **aOR**: adjusted odds ratio; **AS**: axillary surgery; **BrS:** primary breast surgery; **CI:** confidence interval; **CT:** chemotherapy; **ET:** endocrine therapy; **HR:** hazard ratio; **LN:** lymph node; **OS:** overall survival; **N/A:** not applicable; **NR:** not reported; **PT(s):** patient(s); **RT:** radiotherapy.

[1] Hazard ratios are from multivariate analysis, and are presented in relation to non-compliance, e.g. HR > 1 indicates improved overall survival with adherent treatment. The extracted HR were transformed to create the reciprocal if they were presented in relation to compliance.

*5yr OS rates are estimates taken from survival figures as opposed to numbers extracted from tables or written results.

Appendix A. PRISMA checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3 & 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4 & Appendix 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4 & 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4 & 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4 & 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig 1 Page 14
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Page 5 & Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 3 & Figure 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 5–9 Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 9-12
	23b	Discuss any limitations of the evidence included in the review.	Pages 10-11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 12
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 12
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 12

Appendix B

Table B.1. Search terms used in Medline. Performed 07/12/2020.

1	breast neoplasms/
2	early breast cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	1 or 2
4	exp guideline/
5	guideline adherence/
6	practice patterns, physicians'/
7	"delivery of healthcare"/
8	practice guidelines as topic/
9	exp clinical protocols/
10	guideline* adheren*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11	treatment variation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	guideline* complian*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	overall survival.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15	3 and 13 and 14
16	limit 15 to (english language and yr="2000 -Current")

Table B.2. Search terms used in Embase. Performed 06/12/2020.

1	breast cancer/
2	early breast cancer.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3	practice guideline/
4	protocol compliance/
5	clinical protocol/ or antineoplastic protocol/
6	clinical practice/
7	guideline* adheren*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8	treatment variation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9	guideline* complian*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10	clinical outcome/
11	exp cancer survival/
12	exp disease free survival/
13	disease specific survival/
14	exp recurrence free survival/
15	overall survival/
16	1 or 2
17	3 or 4 or 5 or 6 or 7 or 8 or 9
18	0 or 11 or 12 or 13 or 14 or 15
19	6 and 17 and 18
20	limit 19 to (english language and yr="2000 -Current")

Appendix C. Studies excluded from the systematic review after evaluation of the full-text.

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Appendix D. Quality assessment results scored using the Newcastle Ottawa Scale.

	Selection (max 4 stars)				Comparability (max 2 stars)	Outcomes (max 3 stars)			
Study	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demons. that outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total / 9
Andreano et al (2017)	1	1	1	1	2	1	1	1	9
Cheng et al (2009)	0	1	1	1	1	1	1	1	7
Chereau et al (2011)	0	1	1	0	0	0	0	0	2
Dooley et al (2011)	0	1	1	0	0	0	0	0	2
Ho et al (2020)	1	1	1	0	0	1	0	0	4
Hsieh et al (2019)	1	1	1	1	2	1	1	0	8
Kantor et al (2018)	1	1	1	1	2	0	1	0	7
Plavc et al (2019)	1	1	1	0	2	0	0	0	5
Sun et al (2015)	1	1	1	0	1	0	0	0	4
Taubenhansl et al (2020)	1	1	1	0	1	1	1	1	7
Van de Water et al (2012)	1	1	1	0	1	0	0	0	4
Vogsen et al (2020)	1	1	1	1	0	1	0	0	5
Wimmer et al (2019)	1	1	1	0	1	1	1	1	7
Wockel et al (2010)	1	1	1	1	0	0	0	0	4
Yun et al (2007)	1	1	1	0	0	1	1	0	5
Zhao et al (2019)	1	1	1	0	1	0	0	0	4

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