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Chemotherapy and gene expression profiling in older early luminal breast cancer patients: An International Society of Geriatric Oncology systematic review

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Dr Nicolò Matteo Luca Battisti, Dr Nienke De Glas and Dr Enrique Soto-Perez-De-Celis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: all authors.

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Appendix A. Supplementary data

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Abstract

Background: The benefit of chemotherapy for older patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC) is a key area of debate. Gene expression profiling (GEP) may identify patients deriving benefit, but their predictive role has not been established for older adults.

We summarise evidence on efficacy, safety, and quality-of-life impacts of chemotherapy and on GEP use and impact in older HR-positive, HER2-negative EBC patients.

Methods: We conducted a literature search of PubMed and Embase on publications describing prospective studies evaluating chemotherapy in older adults with HR-positive, HER2-negative EBC and on publications describing retrospective and prospective studies evaluating GEP in older adults.

Results: Eight publications on chemotherapy use, including 2,035 older patients with EBC were selected. Only one trial evaluated chemotherapy survival benefits in older adults, showing no benefit. Of four studies comparing different regimens, only one showed the superiority of taxanes versus anthracyclines alone. Those investigating alternative regimens did not show improvements over standard regimens despite significant limitations.

Five publications on GEP, including 445,323 older patients, were included and investigated Oncotype DX. Limited evidence shows that GEP aids treatment decisions in this population. GEP was offered less frequently to older versus younger patients. Higher Recurrence Score was prognostic for distant recurrence, but chemotherapy did not improve prognosis.

Conclusions: In older patients with HR-positive, HER2-negative, chemotherapy survival benefits EBC are unclear and GEP is less used. Although its prognostic role is well established, its predictive role remains unknown.

Keywords

Early breast cancer; Luminal; Gene expression profile; Older; Chemotherapy

1. Introduction

There is substantial debate regarding the benefit of chemotherapy (CT) in older patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC) [1]. Compared with younger individuals, older adults with cancer have a higher competing mortality risk in view of a higher burden of comorbidities and geriatric syndromes [2]. These may mitigate the absolute overall survival (OS) benefits associated with CT. Importantly, older patients are heterogeneous: while some may be fit and have a longer life expectancy (that may justify CT use), more vulnerable individuals may not derive similar survival benefits and have a higher risk of toxicities.

In this context, careful patient selection is key [3]. Gene expression profiling (GEP) can provide additional information on prognosis and predicted benefits of CT in patients with HR-positive, HER2-negative EBC [4–6] and may be a valuable tool to guide treatment decisions also in older patients. GEP may spare CT for many patients while identifying those at higher recurrence risk for whom CT may be beneficial [7,8]. Nonetheless, GEP is not widely used among older adults, and its clinical utility in this population remains unclear [7,9].

A multidisciplinary International Society of Geriatric Oncology (SIOG) task force gathered to systematically review the evidence available on the efficacy of CT and the use of GEP in older patients with HR-positive, HER2-negative EBC (defined based on age cut-offs established by the individual publications).

2. Methods

Two systematic reviews were performed. First, we searched randomised clinical trials (RCTs) presented in full-text publications specifically addressing CT efficacy for older patients with EBC. Second, we searched full-text publications on prospective and retrospective analyses investigating the validity of existing GEP tools in older patients with EBC. We performed both searches in PubMed and Embase (Appendix 1) with the help of a trained librarian of Leiden University Medical Center on September 1, 2021. After selection of references, we performed cross-referencing in order include all relevant articles.

Two independent reviewers (NMLB and NdG) examined the papers from both searches. For part one, we included all papers reporting RCT of CT for EBC and either providing age-stratified outcomes or specifically recruiting older patients. We extracted trial phase, primary and secondary outcomes, inclusion criteria, number of older patients included, proportion of HR-positive tumours, CT regimen and performance status. For part two, we included studies examining the predictive value of GEP tools in EBC and investigating their performance among older patients. We extracted study design, GEP assessed, primary

and secondary outcomes, age and genomic cut-offs, inclusion criteria, age distributions and proportion of patients with node-positive disease.

We evaluated the evidence based on the revised Cochrane risk of bias tool for randomised trials (RoB 2.0) [10] for part one and based on the Quality in Prognostic Studies (QUIPS) criteria [11] for part two.

Owing to the heterogeneity and the high risk of bias in the studies included in the systematic review, a meta-analysis was considered inappropriate. Furthermore, we could not perform a formal heterogeneity testing as the studies included in both parts had different end-points.

3. Results

The selection process is shown in Supplementary Figs. 1 and 2 and the risk of bias details in Supplementary Tables 1 and 2 For part one, eight publications including 2,035 older patients with HR-positive, HER2-negative EBC were selected for inclusion. For part two, five publications including 445,323 older patients were selected.

3.1. Part one: evidence on the impact of chemotherapy for older patients with HR-positive, HER2-negative EBC

Eight full-text publications included in part one reported the findings of five trials; out of these, only the Adjuvant Breast Cancer Chemotherapy Trial compared outcomes for patients receiving CT versus no treatment (Table 1) [12]. The remaining four RCT investigated the use of alternative CT options to spare anthracycline toxicities [13–19]. While three trials compared a taxane-based regimen (nab-paclitaxel/capecitabine [19], docetaxel [17,18] or docetaxel/cyclophosphamide [TC] [13]) with more standard combinations (cyclophosphamide, methotrexate, fluorouracil [CMF] and/or doxorubicin/cyclophosphamide [AC] or epirubicin/cyclophosphamide [EC]), one study investigated the use of capecitabine versus AC or CMF [14–16]. Most trials had survival outcomes as primary end-points [13–18], whereas only von Minckwitz *et al.* investigated treatment compliance and toxicity [19]. Secondary end-points included toxicities in three studies [13–18] and quality-of-life (QoL) in two [14–18]. These studies defined older individuals as ≥65 years, but only von Minckwitz *et al.* included a formal geriatric assessment (GA) [19]; two trials also included an upper age limit cut-off [13,17,18]. These five trials recruited mostly patients with HR-positive EBC (range: 50–76%).

3.1.1. Impact on survival—The Adjuvant Breast Cancer Chemotherapy Trial included patients aged 26–81 years with non-metastatic, pT1–3a pN0-N + EBC and randomised them to six cycles of CMF or four cycles of AC versus no additional treatment given alongside tamoxifen with/without ovarian ablation [12]. The study included 552 patients aged ≥60 years (25% of the trial population), with only 52 (2.6%) aged ≥70 years, and no GA. Subgroup analyses did not document any OS benefit on CT (mostly CMF).

Two of the four studies comparing different CT regimens in older patients, US Oncology Research Trial 9735 and the CALGB 49907, showed improved disease-free survival (DFS) and OS, respectively, with four cycles of TC versus four cycles of AC and with standard

AC/CMF versus single-agent capecitabine, respectively [13–16]. In CALGB 49907, the superiority of AC/CMF over capecitabine decreased over time and not observed in HR-positive disease [14–16]. At 10 years follow-up, worse breast cancer–specific survival (BCSS) was observed in patients receiving alternative regimens, with no effect on OS [16]. Two studies did not document benefits on weekly docetaxel or nab-paclitaxel plus capecitabine compared with six cycles of CMF and/or four cycles of AC [12,17–19].

3.1.2. Impact on safety—Perrone *et al.* and Nuzzo *et al.* demonstrated higher grade ≥2 haematological toxicity and lower non-haematological toxicity rates for patients receiving CMF versus docetaxel [17,18]. Muss *et al.* showed a more favourable safety profile of capecitabine versus standard regimens [14–16]. In Jones *et al.*, older patients experienced more frequently febrile neutropenia on TC versus AC [13]. However, this study did not report information on primary granulocyte-colony stimulating factor prophylaxis. Von Minckwitz *et al.* showed more frequent early treatment discontinuations, dose delays, and dose reductions on nab-paclitaxel/capecitabine versus EC or CMF [19]. Nonetheless, grade 3–5 adverse events were more frequent on standard regimens. No significant impact of geriatric predictors on toxicities and treatment discontinuations was observed in Von Minckwitz *et al.* [19].

3.1.3. Impact on quality-of-life—QoL outcomes (side-effects, future perspective, nausea and vomiting, diarrhoea, appetite loss, hair loss and body image) were worse for patients receiving docetaxel versus CMF in Nuzzo *et al.* and Perrone *et al.* [17,18] Conversely, the impact on QoL was more favourable in those receiving capecitabine versus CMF or AC [14–16].

3.2. Part two: evidence on the use of GEP for older patients with HR-positive, human HER2-negative EBC

Among five publications, Zeng *et al.* and Hartmann *et al.* documented prospective trials specifically enrolling older individuals [20,21]. The other publications describe retrospective analyses (Table 2) [7,22–24].

Most studies investigated Oncotype DX [7,20,22–24], while one investigated Mammaprint [21]. No age-specific validation studies were retrieved on other GEP. Two studies defined high-risk disease based on a Recurrence Score (RS) ≥31 [20,24] and three based on an RS ≥ 26 [7,22,23]. Older age was also defined based on different age cut-offs: in most studies, this was ≥70 years [7,23,24], in three analyses ≥65 [22] and in two ≥ 60 years [20,21]. Only one study investigated distant recurrence rate and BCSS at 10 years as a primary end-point [23]. The other analyses evaluated different outcomes including GEP stratification [21,24], Oncotype DX use [7,22] and impact of GEP on CT use [20,21]. Kizy *et al.* assessed OS and BCSS as secondary end-points only in patients with high RS [7]. No studies included GA in their design.

3.2.1. Prognostic/predictive value—In Stemmer *et al.*, RS discriminate low versus intermediate versus high risk of distant recurrence among patients ≥70 years (RS < 11:

3.0%, 95% confidence interval [CI] 0.4–19.6; RS 11–25: 12.5%, 95% CI 7.0–21.7; RS > 25: 18.2%, 95% CI 9.0–35.0) [23]. Nonetheless, this study did not report age-stratified survival.

Retrospective studies reported contradictory findings despite adjustments. Gulbahce *et al.* showed lower breast cancer–related mortality in patients ≥70 years with RS ≥ 26 receiving CT versus no CT (hazard ratio [HR] 0.63, 95% CI 0.60–0.67) [22]. The other retrospective analyses showed no impacts of CT on prognosis in patients with high GEP scores, nor associations of GEP with survival outcomes in patients ≥70 years [7].

No evidence is available on the predictive value of GEP in older patients.

3.2.2. Impact of GEP on chemotherapy use—In Zeng *et al.*, RS stratification correlates with CT recommendations and use for older patients with EBC (low risk: 11.6%; intermediate risk: 46.0%; high risk: 89.5%) [20]. This study also showed changes in CT recommendations in 14.5% of older patients based on RS, and good compliance with multidisciplinary team recommendations (95.7%). Impacts on chemotherapy decisions have been documented also with Mammaprint use, with overall changes in 18% of patients ≥60 years [21].

Kizy *et al.* also confirmed more frequent CT use in patients ≥70 years with higher RS (RS < 18: 3%; RS 18–30: 16%; RS ≥ 31: 52%) [7].

3.2.3. GEP score distribution in older adults—Fig. 1 shows the GEP category distribution in older patients reported in five studies [7,20,21,23,24]. Swain *et al.* documented a lower proportion of high-risk categorisation based on RS ≥ 31 among patients aged ≥70 years versus <40 years (8.8% versus 14.1%) and a higher median RS in the younger group [24]. This retrospective study documented increasing oestrogen receptor (ER) expression based on age, while progesterone receptor (PR) and invasion gene group expression were similar.

Conversely, a retrospective Surveillance, Epidemiology and End Results (SEER) analysis by Kizy *et al.* showed similar RS distribution in patients aged 18–69 years (RS < 18: 24%; RS 18–30 61%; RS ≥ 31: 15%) compared with those aged ≥70 years (RS < 18: 29%; RS 18–30 55%; RS ≥ 31: 16%) [7].

3.2.4. GEP use in older adults—Two retrospective analyses on SEER data showed lower GEP use in older versus younger patients. In Kizy *et al.* this was 8% versus 18% [7]. Gulbahce *et al.* documented less frequent testing in patients ≥65 years, which persisted regardless of race/ethnicity (odds ratio range: 0.38–0.54) [22].

4. Discussion

This systematic review yields no high-level evidence to support the use of CT in addition to endocrine therapy in older patients with HR-positive, HER2-negative EBC. Although the risk of bias was low for most trials of CT (Table 1), the majority did not provide age-stratified study outcomes and few studies specifically addressed older adults. In addition, these studies investigated different end-points, including RFS, DFS, OS, compliance and

toxicity and performing a meta-analysis was deemed inappropriate. Only the Adjuvant Breast Cancer Chemotherapy Trial investigated AC or CMF versus no CT, revealing no OS gain in older patients with HR-positive, HER2-negative disease [12]. Therefore, prospective evidence does not support OS benefit for older patients with HR-positive, HER2-negative EBC receiving CT [25].

This finding contrasts with retrospective studies showing survival benefits even in the context of comorbidities [26]. However, selection bias is a major limitation of registry analyses [1]. Additional studies included compared 'non-conventional' CT protocols assuming that CT is beneficial [14–19]. However, they did not document improved survival. In an Early Breast Cancer Trialists' Collaborative Group meta-analysis, the positive effect of polychemotherapy on mortality decreased with increasing age (with no details for those aged >69 years) [27]. The impact of contemporary CT regimens on OS in older individuals with ER-positive, HER2-negative EBC is unknown. Dose-dense regimens do not correlate with any benefit in patients ≥70 years [28]. Additionally, RFS and BCSS were worse on capecitabine versus AC or CMF [14–16], while TC improves DFS compared with AC in some older patients [13]. However, these studies enrolled heterogeneous cohorts, including patients with HR-negative disease.

The studies documented a different safety profile of various CT regimens, with more favourable QoL outcomes shown for 'non-conventional' versus standard regimens. Nevertheless, the increased risk of myelosuppression, cardiotoxicity and peripheral neuropathy risk in the older age group is relevant [29]. Although QoL impacts of CT may be temporary in older adults [30,31], this is critical in the context of a more limited life expectancy. Importantly, few studies evaluated the impact of CT on functioning [14–16,32], which is an important outcome for older individuals [33]. The EUSOMA/SIOG recommendations provide guidance on specific chemotherapy regimens in this population [3]: these may include either anthracyclines or taxanes, while combinations can be considered only for carefully selected, fit patients with high-risk disease.

GEP might contribute to identifying patients with HR-positive, HER2-negative breast cancer who are most likely to benefit from CT. However, no evidence supports GEP as a predictive tool for older adults with EBC within their current license. These studies investigated various end-points, including GEP outcomes and use, impacts on recurrence, survival and mortality and effects on treatment decisions. Therefore, conducting a meta-analysis was considered inappropriate. Of note, most trials yielded a significant risk of bias in the study attrition and confounding domains (Table 1). Therefore, more research is warranted on the impact of factoring competing risks of mortality on their performance in this population.

While the RXPONDER study recruited also older individuals [34], MINDACT and TAILORX excluded patients aged ≥70 and ≥ 75 years, respectively [35,36]. Although retrospective and prospective trials have included different age cut-offs and there is lack of consensus on this topic, chronological age does not necessarily reflect tumour biology. Proportions of patients with high RS are similar across age groups [7], consistently with previous data [37]. A high Oncotype DX RS is associated with higher risk of breast cancer recurrence in older adults [23]. However, recent data showed inconsistent impacts

on mortality across age groups [38] and no evidence is available on the association of RS with survival outcomes nor with CT benefits. No age-stratified outcomes have been reported for other GEP tools. Selecting patients based not only on overall health but also on tumour biology might help to identify those who can benefit from CT. However, older individuals are less frequently offered GEP testing compared with younger adults, which reflects their underrepresentation in most validation studies [7,22].

Stratification based on GEP correlates with CT use, with one retrospective study showing improved BCSS in patients ≥70 years with high RS receiving CT [7,20,22]. Two studies showed that Oncotype DX and Mammaprint can shift CT decisions in this population [20,21]. Oncotype DX recently has been shown to have similar impacts in a real-world population of patients aged >70 years with node-positive disease [39]. Nonetheless, the impact of GEP in predicting CT benefits is unclear among older patients. Even if their predictive role was established in this specific population, competing risks of death and a shorter life expectancy may still mitigate the survival benefit of CT. The ASTER 70s study (NCT01564056) will clarify the role of GEP in this cohort [40].

Importantly, an integrated geriatric oncology approach can reduce the risk of severe toxicities in older patients with cancer receiving systemic anticancer therapy [41–43]. In addition, GA can be used to estimate the expected risks of competing mortality, which may support CT decisions. Incorporating GA in the routine care of older patients with EBC is recommended by international consensus [3] and may identify patients most likely to benefit from and tolerate cytotoxics [44].

This review has some limitations. First, few prospective studies comparing outcomes with or without CT for older patients with EBC are available, and GA is not included in most trials [45]. Additionally, these studies did not consider competing morbidity and mortality risks and patient preferences in decision-making, which are critical to define undertreatment and overtreatment in this population [46]. Further studies evaluating the integration of data on overall health derived from the GA along with data on tumour biology derived from GEP and their impact on treatment decisions and tumour- and patient-related outcomes (including functioning, tolerability, and QoL) are warranted.

Additional resources are available to inform decision-making. Online tools incorporating general health parameters may be useful. The Age Gap tool includes comorbidities and functional status to predict the CT benefits in older adults with EBC [47]. Likewise, the PORTRET-tool showed good performance in predicting 5-year recurrence, overall and other-cause mortality among older women with EBC [48]. The EUSOMA/SIOG recommendations are also available to guide the management of older patients with EBC, including specific consensus statements on GEP in this specific cohort [3]. However, even when considering the best information available on tumour biology and on patients' overall health, the integration of relevant end-points for older individuals, such as quality of life and functional independence, with more traditional end-points related to the tumour warrants more investigation [49].

5. Conclusions

There is no strong evidence supporting the use of CT in older patients with HR-positive, HER2-negative EBC. GEP can predict risk of distant recurrence in this cohort. However, their predictive value to support CT decisions warrants further investigation. The interplay between genomic tools and GAs needs to be clarified to improve patient selection and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

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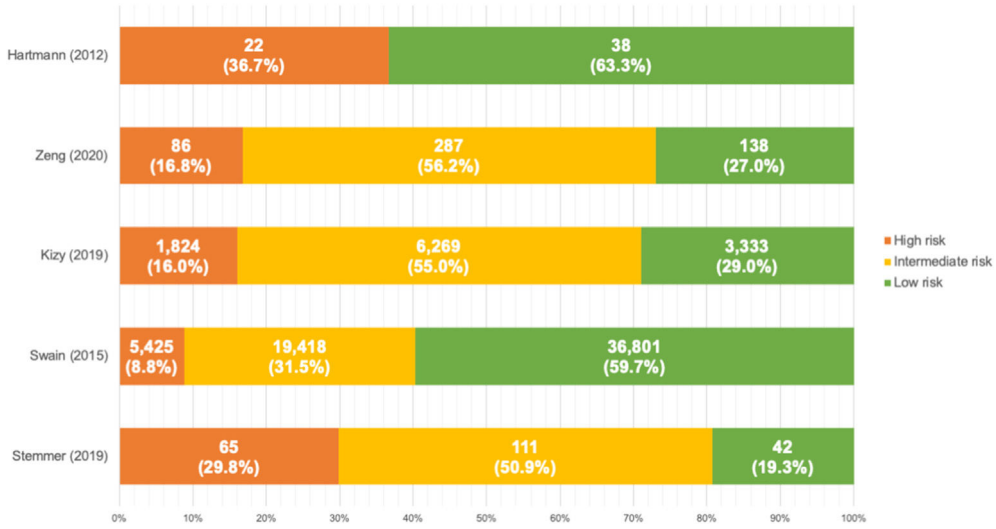

Fig. 1.

Distribution of recurrence risk categories identified in older patients with ER-positive, HER2-negative early breast cancer: summary of systematic review and findings. * Gulbahce (2021) excluded as Oncotype DX Recurrence Risk distribution not reported in the study.[§] Hartmann (2012) includes only two categories (high risk or low risk) as the study investigated Mammaprint.

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Table 1

Studies evaluating the efficacy and safety of chemotherapy in older patients with early ER-positive, HER2-negative breast cancer: summary of systematic review and findings.

Reference	Treatment	Primary end-points	Secondary end-points	Age cut-off	Inclusion criteria	Number of older patients (n)	Age distribution (years)	% HR-positive tumours	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias[a],*
von Minckwitz (2015) [19]	4× EC or 6× CMF versus 6× nPX + capecitabine	Compliance toxicity	Predictive value of geriatric assessment	≥65	Age ≥65 Charlson 0–2 ECOG PS 0–2 Life expectancy ≥5 years pT1/2 pN0/1 and HER2+ ERgrade 3 high uPA, OR Any type pT3/4 pN2/3, CrCl >50 ml/min	391	65–69: 101 (25.8%) 70–80: 287 (73.4%) ≥80+: 3 (0.8%)	65%	Early discontinuation: EC or CMF: 6.6% nPX: 35.8% (p < 0.001) Delays: EC or CMF: 11.1% nPX: 36.8% (p < 0.001) Dose reductions: EC or CMF: 4.5% nPX: 58% (p < 0.001) Grade 3–5 toxicity: EC or CMF: 90.9% nPX: 64.8% (p < 0.001)	No geriatric predictors for toxicity or treatment withdrawal identified	Low risk
Perrone (2015) [18], Nuzzo (2007) [17]	6× CMF versus 4–6x docetaxel (every 4 wks)	DFS	OS QoL Toxicity	65–79	Age 65–79 N+ OR high risk of recurrence (2001 St. Gallen)	299	65–69: 125 (42%), 70–74: 105 (35%), 75–79: 69 (23%)	76%	DFS: HR 1.21 (0.83–1.76, p = 0.32) for docetaxel versus CMF	OS: HR 1.34 (95% CI 0.80–2.22, p = 0.26) for docetaxel versus CMF Grade ≥2 haematological toxicities: CMF: 104 (70%) Docetaxel: 13 (9%) (p < 0.0001) Grade ≥2 non-haematological toxicities: CMF: 29 (19%) Docetaxel: 41 (28%) (p = 0.07) QoL: Docetaxel: worse side-effects, future perspective, nausea and vomiting, diarrhoea, appetite loss, hair loss and body image	Low risk
Muss (2019) [16], Muss (2009) [15], Kornblith (2011) [14]	Capecitabine versus 6× CMF or 4× AC	RFS (noninferiority)	OS Toxicities Adherence QoL Functional status	≥65	Age ≥65 T > 1 cm ECOG PS 0–2	633	65–69: 218 70–79: 389 ≥80: 28	60%	RFS: 0.80 (0.62–0.98) for CMF/AC versus capecitabine, p = 0.0312	OS: HR 0.84 (0.66–1.07) for CMF/AC versus capecitabine (p = 0.1629) BCSS: HR 0.62 (0.39–0.97), p = 0.0348 for CMF/AC versus capecitabine QoL, adverse events, social role functioning,	Low risk

Reference	Treatment	Primary end-points	Secondary end-points	Age cut-off	Inclusion criteria	Number of older patients (n)	Age distribution (years)	% HR-positive tumours	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias[a],*
										fatigue and completion of treatment more favourable on capecitabine	
ABCTCG (2007) [12]	6× CMF or 4× AC versus no CT	OS	RFS	26–81	T1–3a M0	552	>69: 52 (2.6%) 60–69: 500 (25.5%)	40%	OS: 60–69 years: HR 0.97 (0.71–1.32) >69 years: HR 1.2 (0.51–2.86)	Not reported	Some concerns
Jones (2009) [13]	4× AC versus 4× TC	DFS	OS Toxicity	18–75	KPS ≥80 Stage I-III	160	Median: 68 (range 65–77)	70% (across all ages)	DFS: HR 0.70 (0.40–1.24) for TC versus AC	Better OS for TC versus AC HR not reported for >65 Febrile neutropenia: TC: 8% AC: 4%	Low risk

Abbreviations: ABCTCG: Adjuvant Breast Cancer Trials Collaborative Group; EC: epirubicin/cyclophosphamide; CMF: cyclophosphamide/methotrexate/fluorouracil; nPX: nab-paclitaxel; AC: doxorubicin/cyclophosphamide; TC: docetaxel/cyclophosphamide; DFS: disease-free survival; RFS: recurrence-free survival; OS: overall survival; QoL: quality of life; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; uPA: urokinase-type plasminogen activator; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; CrCl: creatinine clearance; KPS: Karnofsky Performance Status; ADL: activities of daily living; CT: chemotherapy.

[a]Risk of bias judgement based on the revised Cochrane risk of bias tool for randomised trials (RoB 2.0).

Table 2

Studies evaluating the use and clinical utility of gene expression profiling in older patients with early ER-positive, HER2-negative breast cancer: summary of systematic review and findings.

Reference	Study design	GEP	Primary outcome	Secondary outcome	Age-specific cut-off (years)	GEP high-risk cut-off	Inclusion criteria	N older patients	Age distribution (years)	N node-positive	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias *
Stemmer (2019) [23]	Retrospective Clalit Health Services registry data analysis	Oncotype DX	Distant recurrence BCM at 10 years	-	≥70	≥26	N0 ER+ HER2- Undergoing Oncotype DX 2009–2009	218	60–69: 473 (34.7%) 70–79: 201 (14.7%) ≥80: 17 (1.3%)	0	10-year distant recurrence risk: RS < 11: 3.0% (95% CI 0.4–19.6) RS 11–25: 12.5% (95% CI 7.0–21.7) RS > 25: 18.2% (95% CI 9.0–35.0) BCM not reported by age		Study participation: + Study attrition: Prognostic factor measurement: + Outcome measurement: + Study confounding: - Statistical analysis and reporting: +
Swain (2015) [24]	Retrospective Genomic Health database analysis	Oncotype DX	RS score	-	≥70	≥31	ER+ 2004–2013	61,643	<40: 13,029 (3.3%) 40–49: 77,590 (19.7%) 50–59: 117,171 (29.7%) 60–69: 124,598 (31.6%) ≥70: 61,643 (15.6%)	32,289 (8.9%)	High RS: <40 years: 14.1% ≥70 years: 8.8% Median RS: < 40 years: 18 40–49: 16 50–59: 17 60–69: 16 ≥70 years: 16	Similar RS distribution Low RS scores in patients aged <40 versus ≥ 70: pN0: 48.3% versus 59.7% pN+: 47.4% versus 61.7% pNmi: 51.5% versus 63.7%	Study participation: + Study attrition: Prognostic factor measurement: ? Outcome measurement: + Study confounding: - Statistical analysis and reporting: +
Kizy (2019) [7]	Retrospective SEER dataset analysis	Oncotype DX	RS use	RS score Chemotherapy use CT impact on OS CT impact on BCSS	≥70	≥26	≥18 years ER+ HER2- Stage I-III 2004–2014	147,107	18–69: 363,876 (71.2%) ≥70 years: 147,107 (28.8%)	10,120 (2.0%)	RS use: 18–69 years: 67.191 (18%) ≥70 years: 11,426 (8%)	RS distribution: 18–69 years: 24% (low) versus 61% (intermediate) versus 15% (high) ≥70 years: 29% (low) versus 55% (intermediate) versus 16% (high) CT use: 18–69 years: 24% (overall) 9% (low)	Study participation: + Study attrition: Prognostic factor measurement: ? Outcome measurement: + Study confounding: - Statistical

Reference	Study design	GEP	Primary outcome	Secondary outcome	Age-specific cut-off (years)	GEP high-risk cut-off	Inclusion criteria	N older patients	Age distribution (years)	N node-positive	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias*
												versus 38% (intermediate) versus 73% (high) ≥70 years: 12% (overall) 3% (low) versus 16% (intermediate) versus 52% (high) CT impact on OS if high RS: 18–69 years: better OS(p = 0.04) ≥70 years: no impact (p = 0.60) CT impact on BCSS if high RS: 18–69 years: better BCSS ≥70 years: no impact	analysis and reporting: +
Zeng (2020) [20]	Prospective observational study	Oncotype DX	Association of RS with CT use CT use based on RS	Change in recommendations post RS Compliance with MDT recommendations	≥60	≥31	≥60 years HR+ HER2- pT1–3 pN0–1 2014–2017	511	≥60: 511 (100.0%)	115 (22.5%)	Association of RS with CT use versus low RS: High RS: OR 252.359; 95%CI, 65.344–974.615 (p < 0.001) Intermediate RS: OR 9.618; 95%CI, 3.978–23.251 (p < 0.001) CT use based on RS: Low RS: 11.6% Intermediate RS: 46.0% High RS: 89.5% (p < 0.001)	Change in CT recommendations post RS: 74 (14.5%) CT: 57 No CT: 17 Compliance with MDT recommendations: Overall: 489/511 (95.7%) Lower for patients aged 70–79 versus 60–69 years: 81.4% versus 93.9% (p = 0.008) 100.0% for patients aged ≥80 years	Study participation: + Study attrition: ? Prognostic factor measurement: ? Outcome measurement: + Study confounding: - Statistical analysis and reporting: +
Gulbahce (2021) [22]	Retrospective SEER dataset	Oncotype DX	RS use	Likelihood of high-risk RS	≥65	≥26	≥18 years Female	236,355	≥65 years: 236,355 (43.8%)	144,884 (26.8%)	Lower odds of RS testing in	CT associated with lower BCM in older patients	Study participation: + Study

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Reference	Study design	GEP	Primary outcome	Secondary outcome	Age-specific cut-off (years)	GEP high-risk cut-off	Inclusion criteria	N older patients	Age distribution (years)	N node-positive	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias*
	analysis of linked to Genomic Health dataset			Predictors of BCM			ER+ pT1–3 2004–2015				older versus younger: OR ranging from 0.38 to 0.54 (p < 0.001) Predictors of lower RS use: PR-, diagnosis year, pN+, pT > 2 cm, grade	with RS ≥ 26: HR 0.63, 95% CI 0.60–0.67 (p < 0.001) Higher BCM in older patients with RS > 26 based on race: Blacks and American Indian: HR 1.30, 95% CI 1.20–1.40 (p < 0.001) Alaskan Natives: HR 1.59, 95% CI 1.15–2.21 (p Z 0.01) CT associated with lower BCM in all races in older patients with RS ≥ 26 PR-status, high grade, pN+, pT > 2 cm associated with higher mortality in older patients with RS ≥ 26	attrition: ? Prognostic factor measurement: + Outcome measurement: + Study confounding: - Statistical analysis and reporting: +
Hartmann (2012) [21]	Prospective observational study	Mammaprint	Mammaprint results	Differences in Mammaprint groups Discordance rate with clinical risk Impacts on treatment recommendations	≥60	Poor prognosis versus good prognosis	≥60 years pT1c-3 60 pN0–1a Grade 2–3 HR+ HER2– 2008-2009	60	≥60: (100.0%)	0 (0.0%)	Good prognosis signature: 38 (63%) Poor prognosis signature: 22 (37%)	No differences in tumour or patient characteristics between signature groups Discordance: Clinical low-risk with poor prognosis signature: 9 (15%) Clinical high-risk with good prognosis signature: 20 (33%) Treatment recommendations after Mammaprint: Chemotherapy: 6 (10%) No	Study participation: + Study attrition: ? Prognostic factor measurement: ? Outcome measurement: + Study confounding: - Statistical analysis and reporting: +

Reference	Study design	GEP	Primary outcome	Secondary outcome	Age-specific cut-off (years)	GEP high-risk cut-off	Inclusion criteria	N older patients	Age distribution (years)	N node-positive	Results primary outcome in older subgroup	Results secondary outcome in older subgroup	Risk of bias*
												chemotherapy: 5 (8%)	

Abbreviations: SEER: Surveillance, Epidemiology, and End Results Program; RS: Recurrence Score; GEP: gene expression profiling; BCM: breast cancer mortality; MDT: multidisciplinary team; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; OR: odds ratio; HR: hazard ratio; OS: overall survival; BCSS: breast cancer-specific survival; CT: chemotherapy.

*Risk of bias judgement based on the Quality in Prognostic Studies (QUIPS) criteria.

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