

Review

# Geriatric Breast Cancer: Staging, Molecular Surrogates, and Treatment. A Review & Meta-analysis

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**ABSTRACT:** Breast cancer (BC) is one of the most frequent cancers in females across the globe. Treatment recommendations for BC patients are primarily driven by patient age, staging and tumor molecular subtype. Thus, we updated the general overview of BC staging, molecular surrogates, and treatment choices for women >70 years based on a systematic study encompassing the years 2013-2023. A PRISMA guidelines and PICO framework were followed, and relevant research articles were searched using different data bases (Web of Sciences, PubMed, MEDLINE, and Scopus). Mixed Methods Appraisal Tool was used for studies quality assessment. The research articles that made it into the systematic review were compiled using qualitative criteria. In the meanwhile, heterogeneity was determined using meta-analysis with RevMan 5.4. We applied a random effects model with a 0.05 significance level. Overall, there were 4151 research articles, after screening only 17 articles with 39,906 patients were included. Conclusion: Elderly patients with breast cancer should be treated differently in an adapted way. The treatment should not be the same worldwide due to different health systems. Molecular surrogates are different in geriatric patients. Surgery is the best option for treatment in this subset of patients. We need to have therapeutic decision appointments for elderly patients with breast cancer. The guidelines and medical authority should be used in the best decision.

**Key words:** Breast Cancer, elderly, molecular subtypes, Cancer staging.

## Introduction

Within the realm of breast cancer research, a significant gap persists in the comprehensive understanding of disease progression, treatment outcomes, and molecular intricacies in geriatric patients aged 70 and above. While substantial progress has been made in breast cancer diagnosis and treatment, a notable disparity exists in the representation of older women within clinical trials and research endeavors. This study seeks to bridge this gap by shedding light on the unique characteristics of breast cancer in the geriatric population, particularly focusing on staging, molecular profiles, and treatment responses [1]. The importance of addressing this gap is underscored by the growing aging demographic worldwide, where a considerable proportion of breast cancer cases occur in women above 70. Current treatment strategies often stem

from studies involving younger patients, potentially leading to suboptimal therapeutic decisions for older individuals.

By elucidating the molecular underpinnings specific to geriatric patients, this study strives to provide valuable insights that can lead to tailored and more effective treatment approaches for this understudied population. Ultimately, the findings from this systematic review and meta-analysis aim to inform clinical practice, enhance treatment outcomes, and improve the quality of life for older women battling breast cancer."

Molecular surrogates refer to specific molecular markers, indicators, or characteristics that are used to indirectly measure or predict certain biological processes, disease states, or treatment responses. In the realm of breast cancer, molecular surrogates often encompass various genetic, genomic, and protein-level factors that

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provide insights into the underlying molecular mechanisms of the disease. These surrogates are particularly valuable in informing treatment decisions, as they can offer a more nuanced understanding of tumor behavior and potential treatment outcomes [2].

In the case of geriatric patients (those aged 70 and above) with breast cancer, the concept of molecular surrogates takes on added significance due to the unique physiological and biological changes that accompany aging. As individuals age, their bodies undergo various alterations, including changes in hormone levels, immune function, and cellular processes. These age-related changes can influence the behavior of breast cancer at the molecular level, potentially affecting how tumors develop, progress, and respond to treatments.

Moreover, the concept of molecular surrogates becomes especially pertinent in the context of tailoring treatment approaches for geriatric patients. Conventional treatment strategies often draw from data obtained primarily from younger patients, potentially overlooking the unique characteristics of tumors in older individuals. By identifying and understanding molecular surrogates that are relevant to geriatric breast cancer, clinicians can make more informed decisions regarding treatment selection, dosage, and duration. This personalized approach can help mitigate potential adverse effects and optimize treatment efficacy, ultimately improving the quality of life for elderly patients.

The concept of 'molecular surrogates' within the realm of breast cancer research holds particular significance in tailoring treatment strategies. However, when considering the geriatric population, a distinctive void becomes evident. In contrast to the extensive exploration of molecular surrogates in breast cancer characterization, staging, and treatment, a marked scarcity of evidence prevails in international literature, specifically among women aged 70 years and above. The absence of research dedicated to investigating molecular surrogates in this demographic underscores a critical gap in our understanding. This gap is of paramount importance, as the distinct physiological changes that accompany aging can significantly influence the behavior of breast cancer at the molecular level. Consequently, the lack of attention to this age group potentially leads to suboptimal treatment strategies extrapolated from studies on younger patients [1]. Our systematic review, situated within this uncharted territory, aims to rectify this gap by shedding light on the unique molecular landscape of breast cancer in geriatric patients. By identifying and synthesizing available data, our study not only highlights the lack of focus on this claim in international literature but also paves the way for future research that could revolutionize the approach to breast cancer treatment in this often-overlooked patient population.

Breast cancer (BC) is the most frequent cancer among women, worldwide [2], while occurrence and death rates sharply rise with age [3]. Finding the best way to treat breast cancer in elderly women is still a challenge [4]. The annual number of new cases of BC in women is close to 2.3 million, accounting for over half of all cancer deaths in women in over 95% of countries [5]. The most current data years (2010-2019) show a 0.5% annual increase in the incidence rates of BC, mainly because of the prevalence of early detection of hormone receptor-positive illness [6]. Death rates from BC, in contrast, have been gradually falling since their peak in 1989, however, at a lower rate 1.3 % annually from 2011 to 2020 than in the preceding decade 1.9% annually from 2002 to 2011 [7]. Human epidermal growth factor receptor 2 (HER2)-negative, hormone receptor-positive BC was detected early in most female patients. It is estimated that less than one percent of women in their 70s and 80s died from invasive BC due to this disease [7, 8]. Except in patients with severe comorbidities or low life expectancy, screening mammography significantly reduces BC mortality in older women [9]. Moreover, there are the American Cancer Society's recommendations, where patients with "excellent overall health" and with a 10-year or longer life expectancy are encouraged to continue cancer screenings [10,11]. However, the American Academy of Physicians and the American Academy of Family Physicians suggest stopping screening beyond age 74 [12]. Though, American College of Physicians, U.S. Preventive Services Task Force, and American Academy of Family Physicians guidelines recommend screening mammography in women 50-74 years old [13, 14] associated with earlier disease stages, while increased survival is yet to be demonstrated. Women at average risk of BC, aged 40 and up, are now encouraged to get a mammogram every year by the National Comprehensive Cancer Network (NCCN) [15,16]. Similarly, according to ESMO recommendation, mammography is indicated for women 50–69 [I, A]. Although the evidence is weaker, women aged 40–49 and 70–74 may benefit from regular mammography [II, B] [17]. Care providers should consider bringing up the topic of screening mammography with their elderly patients, especially those who don't have any major co-morbidities [18]. Discussions about advantages and hazards, tailored to each woman's health situation, are essential for optimizing screening procedures [9]. Once cancer is a disease of aging, health systems need to adapt healthcare to such patients [19]. When treating BC in older women, it is vital to strike a balance between the treatment's curative purpose and the patient's comorbidities and quality of life [20] Patients in their later years have a decreased life expectancy and a different kind of longevity advantage. Patients >70 years should be evaluated using the global

geriatric assessment scale, and scales can be performed by the nursing team [21].

There are gene-profiling models that can predict outcomes. Besides, molecular categorization is the standard for comprehensively characterizing BC the most used being the Oncotype Dx, and Mamaprint; these tests should be used in elderly patients [22-25]. Despite these advances, most doctors still rely on established clinicopathologic features and widely available tumor markers like estrogen receptor (ER), HER2 and progesterone receptor (PR) [26-28]. Additionally, Androgen receptors and p53 are examples of biomarkers that have recently been proven to further stratify these molecular subtypes [28]. Meanwhile, in Western countries at high risk for BC, ER-positive tumors rise in a bimodal fashion, after age 60, luminal A cancers are more common than luminal B tumors with higher proliferation rates [29]. Cancer Centers should have specialized consultations for elderly patients; the optimal treatment might be different from the adequate treatment for this population [30]. Unless there are significant barriers, therapeutic indifference or undertreatment should be avoided, and adequate therapy should be provided [31]. Proactive discussions about treatment with healthcare providers may benefit older women by addressing their unique needs, personalizing cancer care, and easing the healthcare system process [32]. Older women receive less preventative or adjuvant treatment and due to underrepresentation in clinical trials, older women with BC are poorly evaluated and treated [30].

Treatment schedules for healthy women are established, but patients > 75 years are typically not treated according to recommendations due to comorbidities and poor health conditions. Even when cancer is diagnosed at the local or locoregional advanced stage [33, 34], despite some worries and relative contraindications. While reviewing data from the literature and our own experiences, it is crucial to assess how women of advanced age are cared for [35]. It is often up to individual oncologists to make treatment choices in an area of uncertainty for the management of elderly patients with BC. Consequently, this could upsurge the under-treatment risk or, less frequently, overtreatment, which can negatively affect patient outcomes [36]. Alterations in pharmacokinetics and metabolism because of aging are extremely uncommon and it is very important to have the knowledge of current medications to evaluate polypharmacy [37]. Systemic therapy and Adjuvant trastuzumab are preferred over adjuvant systemic therapy alone for older women in good health with HER2-overexpressing BC who have had surgery [38]. Combining HER2-directed therapy with chemotherapy is linked to a modest but real increase in the risk of cardiac dysfunction, especially when an anthracycline-based

regimen is used. Therefore, the prognosis of newly diagnosed BC women must be weighed against the associated risk with treatment (combined) [39]. In addition, CGA or miRNA, even if not used in clinical practice, scoring systems could accurately identify patients who need active or palliative treatment [40]. Adjuvant chemotherapy is given after surgery, often between 4 and 8 weeks after the procedure. When treatment is delayed for more than 12 weeks, it may negatively affect disease-free survival; however, earlier therapy does not necessarily result in a better prognosis [41]. Meanwhile according to ESMO guidelines, neoadjuvant treatment should begin 2–4 weeks following diagnosis and staging, while adjuvant treatment begins 3–6 weeks after surgery [17]. Surgery in elderly patient is often the preferred option because it has the least side effects and complications. The elderly patient should be optimized for surgery in a similar way to that prepared by an athlete [17, 42]. Furthermore, several authors propose the use of neo-adjuvant hormonotherapy to evaluate the response to hormonal therapeutics in the patient, this option should be extended in clinical practice [43, 44]. Moreover, immunotherapy can benefit elderly patients, but they also had higher adverse effects and stopped treatment earlier than younger patients [45]. The toxicity of chemotherapy in addition to complications during treatment and difficulty in completing treatment in full, is associated with loss of years of life due to its negative effects of it [45-47], due to the even if not age-related comorbidities and reduction in organ function, elderly individuals have a lower tolerance for chemotherapy as compared to younger patients [48].

Despite the extensive literature on BC treatment, few studies have examined any potential links to molecular surrogates in older women. We conducted a literature review covering the years 2013–2023, and we offered a revised overview of staging, molecular surrogates, and treatment options for BC in women > 70 years.

## METHODS

The current systematic review and meta-analysis was conducted in the line of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [49].

## Literature search

The search strategy was established according to the participants, intervention, comparators or controls, and outcome (PICO) framework [50]. Population/Participants: This review included older women (>70 years). Intervention: different treatments were used for BC in elderly women. Comparison or control: Other

treatment or control groups used. Outcomes: Updated systematic review and meta-analysis of the literature on the characterization and treatment of BC for elderly women. Different search databases such as Web of Sciences, PubMed, MEDLINE, and Scopus were searched for the relevant research articles using different keywords such as ‘breast cancer’ and ‘older, elder, eldest, elderly’, over 70 years, molecular surrogates,

HER2, ER, PR, Ki-67, EGFR, P53, Androgen receptor, hormone receptor-positive and treatment options like chemotherapy, hormonal therapy, radiotherapy, and other medications' MeSH terms were used, Oncotype Dx, Mamaprint , as well as combinations of those terms (Appendix 1) and selected articles were processed according to PRISMA (Fig.1).

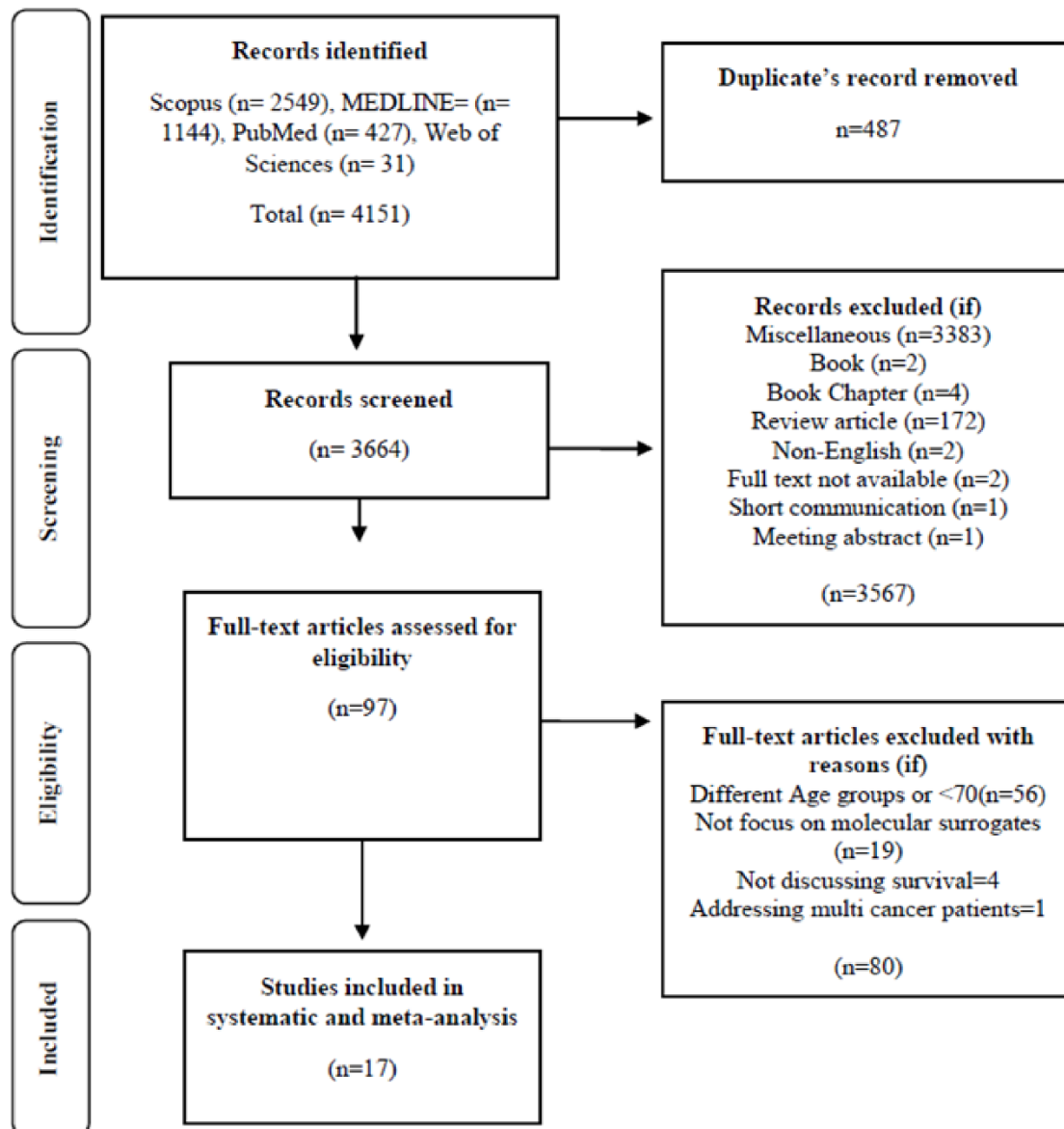


Figure 1. Flowchart for screening of literature.

### Inclusion criteria

The following standards were applied exclusively for selecting studies: 1. Female patients over the age of 70 with a diagnosis of invasive BC (stages I-IV) who were considering or had received different treatments; 2.

Studies identifying molecular surrogates; 3. Studies that have been published in peer-reviewed scientific journals in English; and 4. Studies with patients' perspectives on their experiences with palliative care, alternative medicine, and non-treatment are understudied.

### Exclusion criteria

The following were not considered for inclusion in the study: 1. Publications that do not undergo the peer review process include editorials, reviews, protocols, guidelines, and journals that are not included in citation databases. 2. Research that doesn't account for patients' ages, treatment histories, or outcomes.

### Study selection and assessment

Study titles, and abstracts were all assessed separately. Two reviewers independently evaluated the entire texts of all articles that matched the inclusion requirements, whose opinions were then debated to reach a consensus. If there were any discrepancies, they were discussed with the third independent reviewer to resolved.

### Data extraction

Data extraction was done on the shortlisted studies matching the inclusion requirements. A data extraction form was used to record the data that was extracted after screening the paper's title, abstract, and full text. Two reviewers independently record each study's authors, year of publication, mean age, cancer stage, comorbidities, characterization related data, treatment findings, conclusion, and limitations for a systematic review. While for the meta-analysis: total participants, participants in the BC elderly treatment group, and participants in the control group were used to construct forest plots.

### Quality assessment

Using the Mixed Methods Appraisal Tool (MMAT), quality ratings were determined based on the degree to which each study's methodology met predetermined criteria using the approach described by Charette, McKenna [51]. Studies were classified as either low (scoring  $\leq 3$ ) or high (score  $> 3$ ) depending on the reviewer answered: "yes" (1 point) or "no" (0 points) [52].

### Data analysis

The included articles in the systematic review were compiled utilizing qualitative analysis. The PRISMA checklist was used to conduct a systematic review of pertinent literature, and a step-by-step method for choosing articles was provided. In the meanwhile, meta-analysis was performed using RevMan 5.4 [53] to calculate the Cochrane Q and  $I^2$  values, which quantify trial dispersion. The random effects model was used, with the significance level set at 0.05.

## RESULTS

### Consulted Literature

All research was found in peer-reviewed journals in electronic databases (Scopus, MEDLINE, PubMed, Web of Sciences), which resulted in a total of 4151 relevant publications. There were 487 duplicates that were eliminated. The titles and abstracts of the remaining 3664 papers were then reviewed, and another 3567 were omitted since they were irrelevant to our study. After a thorough evaluation, 80 of the remaining 97 full-text articles were discarded for a variety of reasons (Figure 1). The 17 publications are summarized, and their salient features are listed in tables.

**Table 1.** Qualitative features of included studies.

Ref.	Country	Study design	N	Mean age	Tumor stage (%)					Comorbidities (%)
					0	I	II	III	IV	
[54]	Turkey	Retrospective	83	82	NA	16	41	13	12	Yes
[57]	Singapore	Retrospective	19	84	NA	10.50	36.8 IIa, 26.3 IIb	10.5 IIIa, 15.9 IIIb	0	100
[53]	Turkey	Retrospective	620	75.7	NA	NA	NA	NA	NA	NA
[58]	Chile	Retrospective	366	75.5	NA	32.20	40.10	19.90	7.80	NA
[59]	Canada	Retrospective chart review	762	>70	15.50	50.10	31.90	2.50	NA	NA
[61]	Brazil	Retrospective	70	84	15.40		47.70	33.80	3.10	Yes
[63]	Germany	Retrospective	1292	77.1	NA	NA	NA	NA	NA	29.30
[64]	UK	Retrospective	252	>70	NA	NA	NA	NA	NA	NA
[52]	Turkey	Retrospective	238	75	5	24.80	42.90	27.30	NA	Yes
[62]	Netherland	Retrospective	2390	79.2	NA	NA	NA	NA	NA	Yes
[56]	China	Retrospective	552	>70	NA	NA	NA	NA	NA	Yes
[60]	South Korea	Retrospective	87	74	11.50	29.90	35.60	14.90	8	NA
[55]	China	Retrospective	33,177	77.6	NA	57.70	33.20	9.20	NA	NA

### General characteristics

In the present study, 39.906 patients were reported. Most studies were reported from Turkey [54-56], two studies



from China [57, 58] and single studies from Singapore, Chile, Canada, Brazil, Germany, UK, Netherlands, and South Korea. All studies followed a retrospective study design and collect data using national database registries or hospital records. All studies were focused on elderly patients and included patients >70 years' age. Maximum mean age reported was 84 years [59]. In terms of staging,

there were five stages (0-IV) reported by different included studies [54, 56, 57, 59-62] as indicated in Table 1. Meanwhile, seven studies reported comorbidities (Diabetes, Cardiovascular diseases, hypertension) ranging from 29.30% to 100% patients had comorbidities [54, 56, 58, 59, 63-65].

**Table 2.** Molecular surrogates used for the screening of BC in elderly patients.

Ref.	Molecular surrogates (%)								Metastasis status (%)	
	Hormone receptor+	ER Positive	ER Negative	PR Positive	PR Negative	HER2 positive	HER2 Negative	Ki-67	Present	Absent
[54]	NA	73	20	70	20	NA	NA	NA	12.04	NA
[57]	NA	100	0	52.60	NA	10.50	26.30	NA	NA	100
[53]	NA	75	19.30	67.30	26.90	NA	NA	NA	15	NA
[58]	83.30	NA	NA	NA	NA	12.60	NA	NA	42.70	NA
[59]	NA	75.10	24.90	66.90	33.10	18.90	67.20	NA	NA	NA
[61]	NA	76.90	NA	65.20	NA	13.00	NA	NA	15.70	NA
[63]	NA	87.60	12.40	77.40	22.60	16.10	83.90	100	NA	NA
[64]	NA	NA	NA	26.80	73.20	16.90	83.10	70.70	NA	NA
[52]	NA	79	19.30	70.20	28.60	14.30	85.70	NA	NA	NA
[62]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
[56]	NA	NA	NA	81.90	NA	NA	81.90	NA	NA	NA
[60]	NA	63.20	24.10	48.30	44.80	21.80	71.30	NA	14.90	75.70
[55]	NA	87.50	12.50	76	23.90	10	90	NA	NA	NA

BC=Breast Cancer; NA=Not Available; ER= Estrogen Receptor; PR=Progesterone Receptor; HER2= Human epidermal growth factor receptor 2; Ki=Kiel

### Molecular surrogates

Among the included studies only one study reported Hormone receptor+ molecular surrogate [60]. Maximum 100% ER positive patients were found by Chan, while 63.20% was the minimum ER positive patients [59]. Maximum ER negative 0% patients were documented and 24.90% was maximum ER negative patients [61]. In terms of PR positive 81.90% was the maximum percentage of patients [58] while minimum PR positive was 26.80% patients [66]. Moreover, 73.20% was the maximum PR negative patients reported by Syed, Morgan [66] and

minimum PR negative patients were 20% [56]. Similarly, there were maximum 21.80% HER2 positive patients [62] and 10.50% minimum HER2 positive cases were reported by Chan [59]. Similarly, 90% HER2 negative cases were reported by Wu, Qi [57] while 26.30% was the minimum number of HER2 negative patients [59]. Meanwhile, only two studies reported Ki-67% molecular surrogate [65, 66] (Table 2). Metastasis status of patients is presented in Table 2. Meanwhile, relevant, and advanced surrogates like Oncotype Dx and Mamaprint were not reported in the included studies.

**Table 3.** Subtype reported included studies.

Ref.	Subtype of Breast Cancer			
	Luminal A (%)	Luminal B (%)	Triple negative (%)	HER 2-enriched (%)
[58]	49	33.30	11.70	6
[61]		75.70	20.30	NA
[63]	51	25.80	NA	16.10
[52]	NA	NA	12.10	NA
[60]	21.80	10.30	NA	NA
[55]	81.10	7.10	8.90	2.90

NA=Not Available; HER2= Human epidermal growth factor receptor 2

### Subtype

According to Table 3, there were four different subtypes of BC identified (Luminal A, B, Triple negative, HER2-enriched). Wu, Qi [57] reported maximum 81.10%

luminal A subtype and minimum was 21.80% [62]. Similarly, for luminal B 33.30% was the highest percentage of patients [60] while 7.10% was the least number of patients with luminal B [57]. As for Triple negative there was 20.30% highest percentage of patients

[63] and 8.90% was the least [57]. HER2-enriched maximum patients (16.10%) were reported by Inwald, Ortmann [65].

### Treatment

All the studies in the present review included patients who were using different therapies such as surgery, chemotherapy, radiotherapy, hormonal/endocrine therapy, adjuvant therapy, neoadjuvant therapy. Surgery was the primary method of treating BC in most of the studies [56, 57, 60, 62, 64-66]. While a single study

reported patients using adjuvant and neoadjuvant therapy [54]. The percentage of patients under different treatments with follow-up period are described in Table 4. Meanwhile, in terms of overall survival (OS) 95.2% patients had 7 years of survival [65] and 84.6% patients had Disease Free survival (DFS) (5 years) [60] while 63.2% of patients refused to perform surgery [59]. Furthermore, most of the patients had grade II and III BC while BC was spread to N0 and N1. However, patients with N2 and N3 are also reported (Table 5). Death rate and each study conclusions and limitations are reported in Table 5.

**Table 4.** Different treatments, OS, DFS used by reported patients.

Ref.	Treatment								OS (5 year s) %	DF S (%)	Sur. Ref usal %	Grade (%)				N (%)		
	Total Mastec tomy (Surger y) (%)	Axillary Dissecti on (Surger y) (%)	Radi ation (%)	Chem othera py (%)	Horm onal/E ndocri ne therap y (%)	Adju vant thera py (%)	Neo adju vant thera py (%)	Foll ow- up mon ths								I	II	III
												I	II	III	0	I	II	III
[54]	10	NA	25	16.9	71.08	NA	NA	36	61.9	53.7	NA	16	38	16	30	21	11	5
[57]	5.26	NA	NA	NA	100	NA	NA	28	NA	NA	63.2	NA	NA	NA	NA	NA	NA	NA
[53]	71		Not clear				NA	NA	71- 76	NA	NA	NA	NA	NA	NA	NA	NA	NA
[58]	36.6	62.1	79.1	21.1	NA	NA	NA	57.5 0	76.8	84.6	NA	15.8 0	39.8 0	44.4 0	NA	NA	N A	N A
[59]	NA	Not clear				NA	NA	14	NA	NA	NA	33.4	37.2	29.4	NA	NA	N A	N A
[61]	NA	74.6	3	1.50	20.90	NA	NA	37.1	NA	NA	NA	NA	46.9	36.7	NA	NA	N A	N A
[63]	41.9	NA	26.2	NA	NA	NA	NA	NA	95.2 (7 years)	NA	NA	14.6	63.5	22	NA	NA	N A	N A
[64]	77	NA	5.6%	NA	14.3	NA	NA	37.5	Unc lear	NA	NA	4.6	45.4	50	NA	NA	N A	N A
[52]	NA	59.6	53.7	30.6	82.8	87.4	10.5	41.2	NA	NA	NA	16.4	41.6	26.9	47.9	23.9	12.2	7.1
[62]	NA	NA	Uncl ear	0.16	39.30	NA	NA	57.6	NA	NA	NA	Unclear						
[56]	NA	NA	NA	NA	100	NA	NA	NA	NA	NA	NA	20.8 3	43.6 5	17.3 9	NA	NA	NA	N A
[60]	24.1	2.3	NA	NA	NA	NA	NA	54	NA	NA	NA	Unclear			64.4	17.2	6.9	11. 5
[55]	12.3	NA	47.90	15.89	NA	NA	NA	43.7	Unc lear	NA	NA	29	46.9	24.1	77	17.1	3.8	2.2

NA=Not Available, OS=Overall Survival, DFS=Disease Free Survival, N=Node

### Sub-group analysis

Sub-group analysis was performed (Fig. 2), and there was a difference between treatment and non-treatment groups. There was a significant difference with use of radiotherapy (OR=2.99, 95% CI 0.35-25.19,  $p<0.00001$ ;  $I^2=100\%$ ), with hormonal therapy (OR=9.47, 95% CI 0.72-33,  $p=0.03$ ;  $I^2=79\%$ ) and for Adj chemotherapy (OR=2.23, 95% CI 0.12-43.05,  $p=0.00001$ ;  $I^2=99\%$ ) while there was non-significant different in surgery subgroup (OR=84.46, 95% CI 57.85-123.23,  $p=0.57$ ;  $I^2=0\%$ ). Overall, there was 100% heterogeneity ( $p<0.00001$ ) with OR=6.24, 95% CI 1.43-27.28 (Fig. 2).

### Quality assessment

The MMAT evaluation tool was used to evaluate the study's methodology. The quality of the selected research was consistently good (all values  $>3$ ) (Supplementary Table 2).

### DISCUSSION

Among females, BC is the most prevalent form, and it is also the largest cause of cancer-related mortality globally. The availability of solid clinical and pathological

prognostic, and predictive indications that can guide patient decision-making and therapy options are critical to the effective management of BC [67]. Over the past decade, an assessment of BC studies published in international journals shows that being older is strongly associated with an increased risk of acquiring BC. It is critical to remember that BC in older women has unique clinic-pathological features from the illness in younger

women [68]. Despite the abundance of published material on breast cancer therapy, very few research articles have investigated the possibility of correlations between molecular surrogates and older women. Following the completion of a literature analysis that included the years from 2013 to 2023, we provided an updated summary of the staging, molecular surrogates, and therapy choices for BC in women > 70 years.

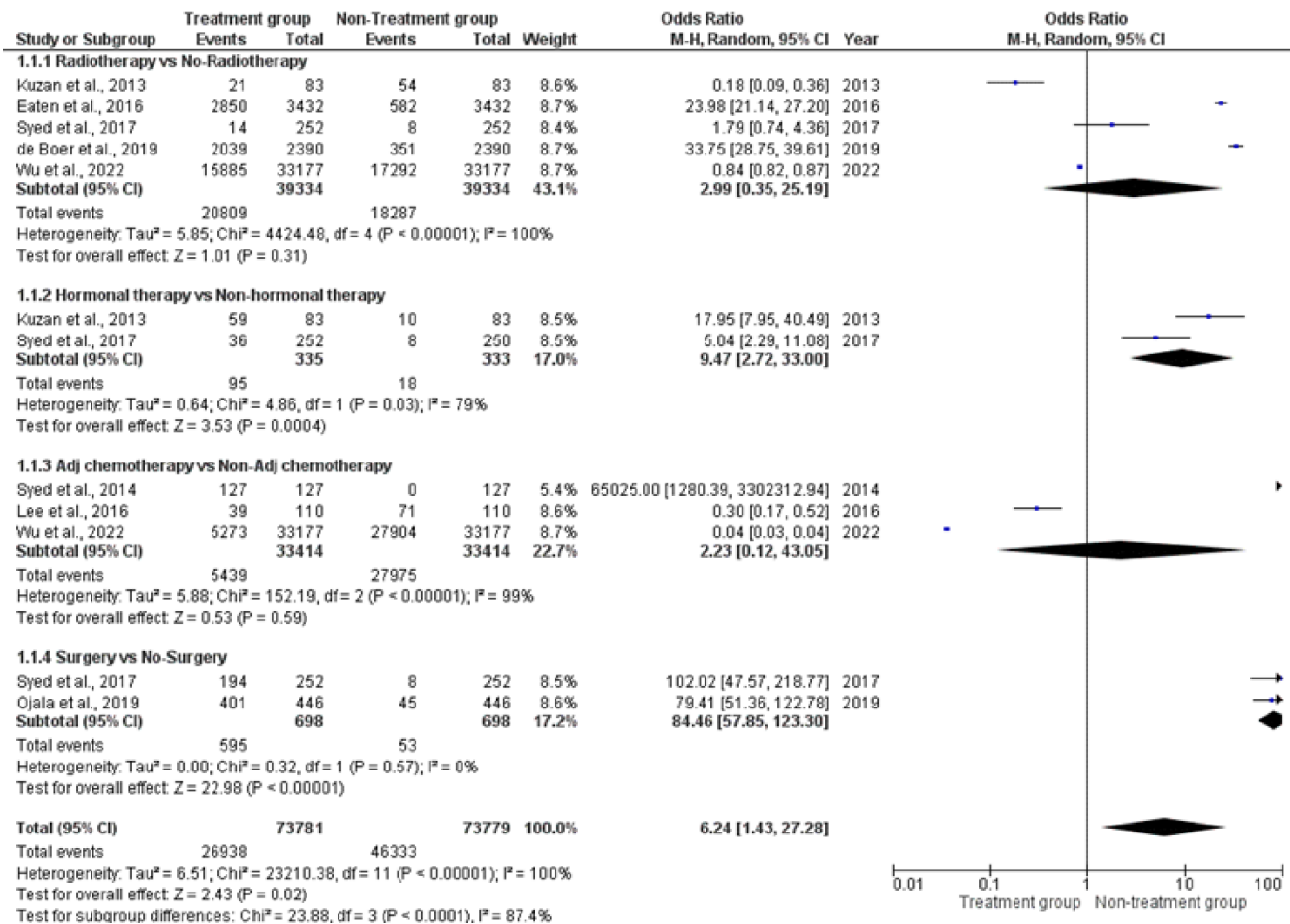


Figure 2. Forest plot for different treatment groups.

In the present study, important molecular surrogates for BC were identified such as ER, PR, Hormone receptor+, HER2 and Ki-67 are useful for diagnosis and prognosis of BC and useful for determining which therapy options is the best for each patient. A question arises, which is why most of the studies reported these most common molecular surrogates. The probable explanation, especially for the ER and PR, can be that it has been known for long that estrogen has a crucial stimulatory role in both the development and progression of BC [69]. Both processes are known to be influenced by estrogen. In addition, ER is considered one of the most crucial prognostic indicators in BC. Meanwhile, it is a member

of a family of nuclear hormone receptors that perform the function of a transcription factor [70]. It is quite plausible that the PR has a role in the development of breast cancer, and it is possible that postmenopausal women are the ones who are most affected by its effects [71]. It is believed that the ER is responsible for regulating PR expression, and the existence of PR expression is seen as evidence of a well-functioning estrogen-ER axis [72]. In most of the occurrences, expression of PR corresponds with ER expression, therefore from a purely practical basis. A strong PR expression in the absence of ER may demand further testing. In situations of early BC, the existence of PR expression is significant from a prognostic



perspective, with patients that are both PR and PR positive having the best result [73]. At the current time, standard practice involves monitoring ER and PR receptor expression. At the same time, HER2 (positive/negative) was also the most reported predictor in the present study, as HER2 gene overexpression is a strong predictive indication, which is also crucial to considered. However, HER-2 low is also used as a new prognostic predictor in the authors' clinical practice. Invasive breast carcinomas, including primary and metastatic, are now routinely tested for HER2 protein overexpression using an immune-histochemical assay. Amplification of the HER2/neu gene is the usual cause of the HER2 protein being

overproduced as a secondary effect. Similarly, Ki67 was shown to be linked with prognosis, overall survival and disease-free survival in meta-analyses conducted by Azambuja, Cardoso [74] and Stuart-Harris, Caldas [75]. Meanwhile, most important, advance surrogates like Oncotype Dx and Mamaprint were not reported in the included studies, which may be due to the strict inclusion criteria. One other reason may be the limited research conducted on these advanced molecular surrogates. Substantially relevant is to align the scientific, clinical, and educational progress with the international health policy priorities [76].

**Table 5.** Conclusions and limitations of included studies.

Ref.	Deaths (%)	Conclusion	Limitations
[54]	24.09	Low fatality rates were found despite undertreating most patients.	NA
[57]	32	Endocrine therapy controlled operable BC in older adults and was well tolerated. Compliance was a major issue.	NA
[53]	NA	Older breast cancer patients behave differently and undergo various therapies.	Study design, small sample size.
[58]	29.40	Young patients had more aggressive illness, worsening DFS. Nonetheless, elderly TN patients have poorer DFS and DSS, suggesting that chemotherapy should not be avoided due to age.	Single center study, Study design, Missing data such comorbidities.
[59]	18.40	80-year-olds had poorer DFS and OS.	NA
[61]	44.30	Brazilian women over 80 with breast cancer survived surgery and hormone therapy.	Small sample size, Study design, missing data such as Ki-67 marker
[63]	NA	It was found that older patients (above 70 years) receive less systemic and local treatment than younger patients (50–69 years).	NA
[64]	48.60	Poor biological and clinical outcomes were seen in geriatric patients with early operable primary breast cancer that lacked the estrogen receptor. Surgery is the standard method for initial care.	NA
[52]	20	Breast cancer patients aged 70-79 received more aggressive therapies, suggesting that treatment choice in patients over 80 years old was likely dependent on age rather than tumor features.	Small sample size, study design, comorbid disease on treatment choice could not be clearly detected.
[62]	0.41	Even in hospitals with limited radiation utilization, locoregional recurrence risk was modest despite 39.3% endocrine treatment. This supports omitting radiation in T1-2N0 breast cancer patients over 75.	Low event rate, residual confounding,
[56]	NA	Adherent endocrine therapy did not significantly affect breast cancer-specific or overall mortality in older women with localized ER-positive breast cancer.	Study design and missing data
[60]	NA	Elderly Korean women have more aggressive clinicopathological and biochemical aspects of breast cancer than all Korean women or elderly women worldwide.	Selection bias, Missing data, small sample size, generalizability.
[55]	16.3 Chemo group, 18.39 non-chemo group	Chemotherapy may improve elderly breast cancer prognosis, especially in chemotherapy-responsive subpopulations.	Missing data

In the present study, four subtypes, such as luminal A and B, HER2-enriched and Triple negative, were identified. These discoveries agree with the results of

Perou *et al.* [77], who used gene expression microarray data on a sample of breast tumors to identify four molecular subtypes of BC: Luminal, HER2-enriched,

Normal Breast-like and Basal-like. Additional research made it possible to subdivide the Luminal group into two subgroups, which were designated as Luminal A and B [78]. Meanwhile, it was also shown that with the incidence of luminal (A, B, and A+B) cancers increased with age ( $p < 0.01$ ), but the proportion of basal-like tumors decreased ( $p < 0.0001$ ) [79]. Similarly, the molecular subtype luminal A is frequently linked to a better prognosis and generally less benefits from chemotherapy [80, 81]. Both characteristics point to a more favorable outcome for the patient. Compared to the other molecular subtypes, this subtype is known to have a more sedentary trajectory and a slower evolution over time [82]. In addition, having a positive status for hormone receptors is not only an indicator of an improved prognosis, but also a sign of how well a patient would respond to endocrine treatment [83]. This comprehensive geriatric approach improves survival outcomes in older adults [84].

Staging for BC is essential because it provides crucial information about the extent and severity of the disease, which helps doctors determine the best course of treatment for the patient. Staging is the process of classifying cancer based on its size, whether it has spread to nearby lymph nodes, and whether it has spread to other parts of the body. In the present study, there were five of 4 BC stages (0-IV) identified, and most of the patients had stage II and III BC as well as Grade II and III. In addition, BC spread to N0-N3, which may be due to delay reporting and under-report worrisome symptoms and lesions to their physicians. This may lead to a later diagnosis of BC at a more advanced stage, with presumably fewer treatment choices and worse results [42]. Our findings are in line with another study and revealed that diagnosis of stage II or III BC was more prevalent (39.2%) among individuals aged  $>80$  [85]. Another study also supports our findings that elder women usually had stage II or III BC [86]. One may ask the reason why stage II and III BC is more prevalent in the present study. This may be due to some contributing factors such as screening, comorbidities, delayed screening or treatment or may aggressive tumor characteristics. However, it is crucial to remember that every instance of BC is distinct and may have a different set of underlying causes. Nevertheless, due to the patients or the physician preferences, we acknowledge that older patients are less frequently included in clinical trials [87]. So, it is critical that all women, even older women, get earlier adequate screening, diagnosis, and treatment for breast cancer.

Treatment choices for BC diagnosed at an early stage must weigh the benefits of reduced recurrence risk from certain medicines against the risks of treatment-related toxicity, which may be worsened in older patients due to physiological decline or comorbidities [88]. In the present study, patients undergoing a variety of treatments were

included in all the papers that were considered for this assessment. These treatments included surgery, radiation, chemotherapy, hormonal and endocrine therapy, adjuvant therapy, and neoadjuvant therapy. In most of the research, surgical procedures were used to treat individuals diagnosed with BC (Table 4). We can inquire into the reason why most of the studies that reported surgical procedures are the best for elderly BC. The possible justification can be that both OS and BCSS were higher in older individuals who had surgical treatment [89]. The illness was well controlled both locally and regionally, most likely due to an increased incidence of surgical therapy. This elderly patient group seemed to be a good candidate for surgical therapy, which appeared safe [89]. Though, according to the sub-group analysis in the present study, there was a difference between treatment and non-treatment groups as there was the significant difference ( $p < 0.01$ ), with use of radiotherapy, with hormonal therapy. However, for Adj chemotherapy, there was non-significant different ( $p > 0.01$ ) in surgery subgroup (Figure 2). The reason for a non-significant difference between surgery and non-surgery in the present study might be the very limited number of research articles addressing surgery as the best option, and without the required data for meta-analysis. In contrast, the study conducted by Morgan [90] revealed that surgery for BC is entirely risk-free for patients  $> 70$  years, and there is no mortality rate associated with the procedure among the 2816 patients who underwent the surgery. However, when dealing with older patients, the therapeutic approach must also consider their life expectancy, and other conditions that may endanger their well-being. The physical state categorization developed by the American Society of Anesthesiologists (ASA) may be used by the surgeon or the anesthesiologist to determine whether the surgical operation or the anesthetic will be safe for the patient [91]. When assessing the efficacy of breast cancer treatments, both OS and DFS are crucial metrics to consider as in the present study patients showed good OS and DFS rate (Table 4). However, these are not the only metrics that should be considered when deciding which treatment option is best for a certain patient. Other considerations, such as QoL, side effects from therapy, and personal preferences, play a relevant role.

The present investigation has several limitations. Firstly, due to the paucity of information on Ki67 expression, Dx, Mamaprint, and other comprehensive molecular markers. Maybe it justifies the fact that almost none of the included study defines Dx and Mamaprint as a predictor for BC, but we are only able to classify the patients into one of the four IHC-defined breast cancer subtypes. Secondly, we have only included articles in English to avoid language biasness. So, we may have missed data regarding other molecular surrogates (Dx,

Mamaprint) or any other advanced biomarkers. More data on the impact of regular mammography screening on quality-of-life outcomes, morbidity outcomes, and mortality outcomes, as well as the usage of current imaging technology and BC treatments, would be beneficial. Data for specific groups of women, such as older women, or groups based on race or ethnicity, access to screening, or the prevalence of co-morbidities, may help to enhance screening methods. The examples include

older women. Despite the lack of conclusive research on how new technologies like tomosynthesis affect screening results, their usage is expanding rapidly in developed countries. While several international scientific societies and journals draft guidance to the older adults with cancer inclusion, there are numerous regulatory global initiatives to give such a vulnerable group of patients access to efficient clinical trials [92].

**Table 6.** Characteristics of breast Cancer in the elderly.

Ref	Invasive Ductal Carcino ma (%)	Invasive Lobular Carcino ma (%)	Other types (%)	IHC				Subtype				HE R 2-posit ive	Grade			Stage				
				ER	PR	HE R2	Ki67	Lumi nal A	Lumi nal B	Triple negati ve	1		2	3	0	I	II	III	IV	
[54]	70	8	20	73	70	NA	NA	NA	NA	NA	NA	16	38	16	NA	39	32			
[57]	NA	NA	NA	0	52.6	10.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	10.5	36.8 IIa, 26.3 IIb	10.5 IIIa, 15.9 IIIb	0	
[53]	75.3	8.5	11.5	75	67.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
[58]	72.8	11.8	15.4	NA	NA	12.6	NA	49	0.333	11.7	6	15.8	39.8	44.4	NA	32.2	40.1	19.9	7.8	
[59]	68.9	11.4	5.8	75.1	66.9	18.9	NA	NA	NA	NA	NA	33.4	37.2	29.4	15.5	50.1	31.9	2.5	NA	
[61]	74.3	Unclear	Uncl ear	76.9	65.2	13	NA	75.7	20.3	NA	NA	NA	46.9	36.7	15.4		47.7	33.8	3.1	
[63]	NA	NA	NA	87.6	77.4	16.1	NA	51	25.8	NA	16.1	14.6	63.5	22	NA	NA	NA	NA	NA	
[64]	84.2	2.5	10.5	NA	26.8	16.9	NA	NA	NA	NA	NA	4.6	45.4	50	NA	NA	NA	NA	NA	
[52]	65.5	9.2	25.2	79	70.2	14.3	NA	NA	NA	12.1	NA	16.4	41.6	26.9	5	24.8	42.9	27.3	NA	
[62]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Radioth erapy group=3 0.4; No radiothe rapy group=3 2.2	Radioth erapy group=4 8.8; No radiothe rapy group=4 2	Radioth erapy group=2 0.8; No radiothe rapy group=2 5.8	NA	NA	NA	NA	NA	
[56]	NA	NA	NA	NA	81.9	NA	NA	NA	NA	NA	NA	20.83	43.65	17.39	NA	NA	NA	NA	NA	
[60]	79.1	2.3	63.2	63.2	48.3	21.8	NA	21.8	10.3	NA	NA	Unclear			11.5	29.9	35.6	14.9	8	
[55]	NA	NA	87.5	87.5	76	10	NA	81.1	7.1	8.9	2.9	29	46.9	24.1	NA	57.7	33.2	9.2	NA	
Average	73.76	7.67	12.63	80.06	65.49	14.9	NA	55.72	19.13	13.25	8.33	18.83	44.77	29.65	11.85	34.89	38.57	19.94	4.73	
TNM (%)														Neoadjuvant Hormonotherapy (%)		Neoadjuvant Chemotherapy (%)				
T							N					M								
Tis	T1	T2	T3	T4	N0	N1	N2	N3	N4	M0	M1	Yes	No	Yes	No					
NA	16	41	13	12	30	21	11	5	NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
15.5	64.5	31.4	4.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2.36	NA					
16.9		47.7	13.8	12.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
NA	35.3	46.2	8.4	8	47.9	23.9	7.1	7.1	NA	NA	NA	unclear 10.5								
NA	Radiother apy group=71 .1; Non radiother apy group=60 .7	Radiother apy group=28 .9; Non radiother apy group=39 .3	NA	NA	Unclear				NA	NA	NA	NA	NA	NA	NA					
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
11.5	39.1	35.6	6.9	6.9	64.4	17.2	6.9	11.5	NA	92	8	NA	NA	NA	NA					
0	63.7	29	4.6	2.6	77	17.1	3.8	2.2	NA	NA	NA	NA	NA	NA	NA					
10.98	43.72	38.48	8.47	8.4	54.83	19.8	8.48	6.45	NA	92	NA	NA	NA	NA	0.02					

Surgery		Adjuvant Hormonotherapy (%)		Adjuvant Chemotherapy (%)		Radiotherapy		Treatment refusal (%)	Treated in Specialized Geriatric Center	ECOG status	Geriatric 8 Assessment	Vulnerable Elderly Survey-13
Mastectomy	Breast conserving surgery	Yes	No	Yes	No	Yes	No					
										1 to 5		0-2
10.00	17	NA	NA	16.9	NA	25	75	NA	No	NA	NA	NA
5.26	NA	NA	NA	NA	NA	NA	NA	63.2	Unclear	NA	NA	NA
71.00	10.5	30.3	NA	69.8	NA	44.8	NA	NA	No	NA	NA	NA
36.60	NA	NA	NA	21.1	NA	79.1	NA	NA	No	NA	NA	NA
NA	Unclear	76.5	NA	NA	NA	77.43	NA	NA	Yes	NA	NA	NA
NA	25.71	NA	NA	NA	NA	34.28	65.71	NA	No	NA	NA	NA
41.90	52.9	NA	NA	NA	NA	26.2	73.8	NA	NA	NA	NA	NA
77.00	NA	NA	NA	NA	NA	5.6	NA	NA	No	NA	NA	NA
NA	32.8	Unclear 87.4				53.7	44.1	NA	No	NA	NA	NA
NA	NA	Unclear	Unclear	NA	NA	85.31	14.68	NA	No	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	No	NA	NA	NA
24.10	58.6	NA	NA	NA	NA	NA	NA	NA	No	NA	NA	NA
12.30	NA	NA	NA	NA	NA	47.9	52.1	NA	No	NA	NA	NA
41.47	32.92	15.53	NA	29	NA	40.3	54.2	63.2	7.7	NA	NA	NA

To resume it we enclose Table 6 with more specific data. The present study extensively investigates various facets of breast cancer treatment among elderly patients, encompassing molecular surrogates, subtypes, treatments, and outcomes. While the study provides valuable insights into the characteristics of the included research, it does not explicitly offer detailed findings or conclusions that directly establish surgery as particularly suitable for this age group. The study focuses on presenting a comprehensive overview of the collected data rather than delving into specific treatment rationales. Consequently, the assertion that surgery is advantageous for elderly breast cancer patients might be inferred from the broader context of the study's findings [1], but definitive support for this claim is not explicitly presented within the study itself. To address this gap, further research and literature could be explored to provide a more robust foundation for the conclusion regarding the suitability of surgery for elderly patients with breast cancer, compared to their younger counterparts [93].

While our investigation primarily focused on molecular surrogates, subtypes, and staging, it's worth noting that surgical interventions have emerged as a prominent consideration within the therapeutic landscape. The available data suggest that surgical procedures play a significant role in the management of breast cancer in older individuals. Various studies in our analysis indicated that surgical treatment, often in conjunction with other modalities, was associated with improved overall survival and controlled disease progression in this age group.

Through an examination of multiple research articles spanning the years 2013 to 2023, we revealed that surgery holds a significant place in disease control and survival enhancement among elderly breast cancer patients. Our findings indicate that surgical procedures were commonly employed and associated with favorable outcomes, including improved overall survival and disease-free survival rates. These results highlight the essential nature

of surgical considerations in clinical decision-making, emphasizing its potential to extend life expectancy and enhance the quality of life for elderly breast cancer patients. As a result, our research holds the potential to influence clinical practices and treatment guidelines, advocating for a more pronounced incorporation of surgery within the therapeutic repertoire for elderly breast cancer patients. However, it's important to acknowledge that the suitability of surgery should be carefully evaluated in alignment with the unique molecular subtypes and clinical profiles of older patients, as our study findings have shown considerable variation among available therapies. Thus, while surgery is an integral component, its application must be balanced with considerations of patient-specific characteristics and preferences [1], in addition to the broader treatment options available.

No matter how old a patient is, in the current era, staging and molecular subtype are the most accurate predictor of the result. That's why we updated an earlier description of BC staging, molecular surrogates, and treatment choices for women > 70 years based on a literature analysis encompassing the years of 2013 to 2023. We found that molecular markers such as ER, PR, Hormone receptor+, HER2, and Ki-67 are useful as prognostic indicators for BC. In addition, luminal A and B, HER2-enriched, and Triple negative were identified as the four major subtypes. There were four BC stages (0-IV) identified, and most of the patients had stage II and III BC as well as Grade II and III. In addition, BC spread to N0-N3. Possible treatments include surgery, radiation, chemotherapy, hormonal and endocrine therapy, adjuvant, and neoadjuvant therapy. Studies treating individuals with BC mostly used surgical procedures. Overall, there was substantial variation among available therapies. In general, patients showed good OS and DFS. However, the differences between the surgery groups were not statistically significant. Surgery should be carefully evaluated in older women with unfavorable

molecular subtypes because it has the potential to considerably change disease-related prognosis. By learning more about the connection between tumor biology, age-specific therapy, and outcomes, we might perhaps refine our surgical approach. Breast cancer treatment is different worldwide because health systems and Global Geriatric Scales are different. Time to therapeutic decision, treatment and meetings should be critical to assist these patients, and that would bring clinical and economic benefits for patients and countries.

## Conclusion

The study's findings have far-reaching implications for transforming real-world clinical practices and treatment strategies in the realm of elderly breast cancer care. The identification of molecular surrogates such as ER, PR, Hormone receptor status, HER2, and Ki-67 as potent prognostic indicators offers a personalized avenue for tailoring treatments based on individual patient biology. This precision-focused approach holds the potential to amplify treatment responses while curtailing unnecessary interventions.

Furthermore, the delineation of distinct molecular subtypes like luminal A and B, HER2-enriched, and Triple-negative provides a foundation for targeted therapeutic approaches. By aligning treatment choices with the specific subtype, clinicians can potentially elevate treatment outcomes and mitigate adverse effects. The study's spotlight on the pivotal role of surgery in bolstering disease control and survival among elderly patients underscores the critical importance of surgical considerations in clinical decision-making.

The implications of our study extend into the realm of treatment guidelines, where the integration of molecular markers such as ER, PR, HER2, and Ki-67 can heighten the precision of diagnostic and prognostic evaluations. This, in turn, can drive personalized treatment recommendations that minimize unnecessary interventions while maximizing therapeutic benefits. The study's emphasis on the significance of luminal A and B subtypes, correlated with improved prognosis, advocates for a more robust incorporation of these factors into treatment decisions.

Additionally, identifying specific subgroups that might derive greater benefit from hormonal therapy than aggressive chemotherapy signifies a shift towards more targeted and less taxing interventions. In the meanwhile, some studies refer that overall, survival amongst older women was worse when receiving primary endocrine therapy [94].

Ultimately, this research holds the potential to catalyze a multidisciplinary approach in healthcare delivery. Collaboration among oncologists, surgeons,

radiologists, and geriatric specialists becomes pivotal to ensure comprehensive care that addresses both the complexities of cancer and the unique needs of elderly patients [95]. These findings empower clinicians with evidence-backed insights while empowering patients to actively participate in shared decision-making throughout their treatment journey. As we chart the path ahead, the study's ramifications could translate into an enhanced quality of life, improved treatment outcomes, and a more streamlined healthcare experience for elderly breast cancer patients [96].

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## Competing Interests Statement

The Authors declare no Competing Financial Interests and Non-financial Interests.

## Supplementary Materials

The Supplementary data can be found online at: [www.aginganddisease.org/EN/10.14336/AD.2023.1002](http://www.aginganddisease.org/EN/10.14336/AD.2023.1002).

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