Peer Review File

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Review Comments

Reviewer A

This is a comprehensive review but a few issues are missing.

1. What about personal preference in treatment which may be a greater issue for the elderly, especially if travel to treatment is an issue.

Reply 1: Thank you for the comment. We have added a section (page 4, line 79 - 93) on elderly patient's preferences of care. We included data including a systematic review and other studies showing that elderly patients place a high priority over maintaining quality of life and independence. It was also highlighted that patients' and their physicians' perceived preferences are not uncommonly discordant.

"While it is always important to understand patients' preferences and priorities before making treatment decisions…. highlighting the critical need to elicit and incorporate patients' preferences when making treatment decisions (11)."

2. What about issues of competence in understanding treatment?

Reply 2: Patients' and their caregivers' competence in understanding treatment are important. This assessment should be included in the comprehensive geriatric assessment (CGA) which includes the evaluation of the patient's cognitive and psychological function. A section on geriatric assessment is added to elaborate on the essence and significance of the CGA in assessing patients' ability to understand and tolerate treatment (page 3, line 62 - 69).

"In treating elderly patients with cancer, oncologists should incorporate the results of the CGA to develop an integrated and individualized plan. This involves estimating the risks for adverse outcomes, identifying and addressing non-oncologic problems including cognitive, psychological and physical function to ensure ability to comprehend and tolerate treatment, and providing information to patients and caregivers to guide shared decision-making for treatment (6). The CGA forms the core of clinical decision-making, as it best identifies the older adults who are resilient enough to receive intensive cancer treatments and those who are frail and vulnerable (7)."

3. Is the radiotherapy toxicity quoted up to date with the shorter number of fractions now used.

Reply 3: The FAST-Forward trial and the FAST trial, both using five fractions, were cited and described in the radiotherapy section (page 7, lines 163 - 169). There were no age-specific toxicities data available for these trials.

" The FAST-Forward trial, in which more than 50% of the patients were aged 60 years or older, showed that an abbreviated course of radiotherapy to the breast or chest wall (26 Gy in five fractions over one week) was non-inferior to the standard conventional fractionation (40 Gy in 15 fractions over 3 weeks) in terms of local

control and toxicity profiles (23). The FAST trial, comparing 28.5 Gy in one-weekly 5 fraction schedule with 50 Gy in 25 fractions, showed that there were no significant differences in normal tissue effects at 10 years of follow up (24)"

4. Are there any indications for shorter treatments?

Reply: Yes, for breast or chest wall radiotherapy, an abbreviated course of radiotherapy using five fractions instead of conventional fifteen fractions reduces the treatment burden in terms of the time and financial commitment required for longer courses of radiotherapy. (page 7-8, lines 163 - 171)

" The FAST-Forward trial, in which more than 50% of the patients were aged 60 years or older, showed that an abbreviated course of radiotherapy to the breast or chest wall (26 Gy in five fractions over one week) was non-inferior to the standard conventional fractionation (40 Gy in 15 fractions over 3 weeks) in terms of local control and toxicity profiles (23). The FAST trial, comparing 28.5 Gy in one-weekly 5 fraction schedule with 50 Gy in 25 fractions, showed that there were no significant differences in normal tissue effects at 10 years of follow up (24). The accelerated radiotherapy regimen offers a more palatable alternative for elderly patients, as it reduces the treatment burden in terms of the time and financial commitment required for longer courses of radiotherapy."

5. Co morbidities and issues of concomitant meds should be addressed

Reply 5: Patient's comorbidities and concomitant medications should be reviewed in the CGA, highlighted under the geriatric assessment section on (page 3, lines 58 - 61).

" International geriatric oncology guidelines suggest that CGA should include the evaluation of the patient's comorbidities, medications, physical, cognitive, psychological, and social functioning, frailty, falls, and nutritional status (5,6)."

6. Recent publication should be included. Targeted Oncology (2024) 19:303–320 https://doi.org/10.1007/s11523-024-01046-zSYSTEMATIC REVIEW Palbociclib in Older Patients with Advanced/Metastatic Breast Cancer: A Systematic ReviewEtienne Brain et al.

Reply 6: Thank you for the reference. We have included this review in (page 7, line 151 - 155) under the endocrine therapy section.

"Another systematic review on palbociclib found similar treatment efficacy regardless of age. Notably, global quality of life was maintained in both older and younger patients. Despite higher rates of dose modifications, treatment interruptions and discontinuations in older patients compared to their younger counterparts, the PFS and OS outcomes were not adversely impacted (21)."

7. What about standard geriatric assessments in oncology. Should they be done

Reply 7: Yes, geriatric assessments should be done to guide treatment decisions in older patients. We have added a section on geriatric assessment which included the ASCO and ISGO recommendations and reported data from a randomized controlled

trial to demonstrate the benefit of CGAs (page 3, line 56 - 76).

"Conducting a geriatric assessment at baseline and at regular intervals is important in the care of elderly cancer patients (5,6). International geriatric oncology guidelines suggest that comprehensive geriatric assessment (CGA) should include the evaluation of the patient's comorbidities, medications, physical, cognitive, psychological, and social functioning, frailty, falls, and nutritional status (5,6)…..The integrated oncogeriatric care consisted of CGA and coordinated care between oncologists, geriatricians and multidisciplinary teams."

Reviewer B

Overview
In this mini review, the authors aim to discuss the unique challenges that older breast cancer patients face in survivorship, focusing on treatment-related toxicities in breast cancer. This is an important topic, as older patients have not been well-represented in clinical trials for breast cancer treatments. Older patients, on average, have a greater number of comorbidities and lower performance status, so it is important to understand whether this specific age group may experience greater adverse events or side effects from standard breast cancer therapies. Overall, I think this is an important topic which is appropriate to be included in this Special Series for the Annals of Palliative Medicine. However, there are several aspects of the manuscript that warrant further consideration, which I expand on in the comments provided below.

(1) Writing Quality – Needs Work
To be completely honest, it was difficult for me to focus on evaluating the substance of this manuscript because I was so distracted by the poor writing. Although the writing quality can be mutually exclusive from the research quality (i.e., high quality research but poorly written manuscript), it does make the paper more difficult to follow when there are this many issues. Here are some examples:

• In the "Surgery" section, in the first 3 sentences, the authors summarize the findings of the UK study (Morgan, et al.). Then in the fourth sentence, when the authors write, "In addition, mastectomy was found to increase…", this makes it sound like they are still discussing the findings of the UK study, when they are actually citing the Swedish study. This problem is repeated all throughout the paper – they move from discussing one paper to discussing another, without notifying the reader that they are discussing a new study. The readers often have to make this inference based on looking at the reference numbers. Each time the authors begin discussing the findings of a new study that has not been previously mentioned, the authors should describe the basics of that study. The authors do a nice job of this in line 143: "A population-based study of 29,102 Medicare patients showed that…". Do this throughout the paper.

Reply: Thank you for the detailed comment. We have adopted this format throughout the paper as suggested.

• Right now, the reference numbers are not consistent with the order in which they

appear in the manuscript.

Reply: Thank you. We have improved this issue in the revised manuscript.

• Spelling inconsistencies throughout. For example, sometimes they use “et al.” and other times they use “et al”. Additionally, they switch back and forth between spelling out “less than” and using symbols such as “<”. Choose one method and stick with it.

Reply: Thank you. We have addressed this inconsistency in the revised manuscript.

• Inconsistent use of commas and semicolons in lists, for example, this sentence switches in the middle: “Nevertheless, AI can impair patients’ abilities to perform activities of daily living because of its associated arthralgia and myalgia, exacerbation of osteoporosis due to increased osteoclastic activity and bone density loss, change in lipid profile (10); cognitive impairment (11); all of which are major concerns to older patients.”

Reply: Thank you. We have addressed this inconsistency in the revised manuscript.

• In lines 134-136, the authors write, “The study revealed that older age was significantly associated with a decrease in vital capacity and forced expiratory volume 1 during long-term follow-up.” What does the “1” mean in this sentence?

Reply: Thank you. It was “forced expiratory volume in 1 second” (FEV1). We have revised the section on radiation toxicities and rephrased it to “Old age was significantly associated with worse lung function parameters and higher rates of radiation fibrosis and dyspnea.” (page 8, line 184 - 185) for better flow of the paper.

• Often times when discussing a study, the authors write, “It was found…” without providing any description of the study that they are referring to. Here is an example: In lines 83-85, the authors write: “It is also important to note that the 1-year mortality of hip fracture was as high as 21.1% with usual care in patients 60 years old and above (12).” This should be re-written to: “It is also important to note that, in one prospective study that followed 758 hip fracture patients aged 60 years and older, the 1-year mortality of hip fracture was as high as 21.1% with usual care (12).”

These are just several examples, but there are more. I think the manuscript would benefit from someone with more editorial talents reviewing the manuscript and helping the first author make grammatical/stylistic revisions. There should be someone in the co-author list who can play this role. Again, this is not a criticism of the research itself, but it greatly impacts the reader’s ability to process and comprehend the research.

Reply: Thank you for the detailed comment. We have made edits based on all the comments listed above. When discussing a study, we gave a brief description of the study prior to reporting the results. We improved the consistency of the use of punctuations and symbols. The specific phrases above were all edited as suggested.

(2) Questionable Added Value of the Manuscript
It is unclear to me how this manuscript differs from recent work that has already been

published on this topic, such as the following review published in 2022: Abdel-Razeq H, Abu Rous F, Abuhijla F, Abdel-Razeq N, Edaily S. Breast Cancer in Geriatric Patients: Current Landscape and Future Prospects. Clin Interv Aging. 2022 Sep 28;17:1445-1460. doi: 10.2147/CIA.S365497. PMID: 36199974; PMCID: PMC9527811. This review is more thorough and includes many more studies, which makes me question why those studies were omitted from this review. Maybe you could position this review as a shorter summary for clinicians with less time to read a long review. It just needs to be positioned in some way that shows this work is adding new value to the existing literature. The value and importance of this research study would be much clearer if the authors explained precisely how their work differs from previous work already published on this subject.

Reply: Thank you for the insightful comment. We have better explained our aim to provide an updated comprehensive overview of the current guideline recommendations for geriatric cancer patients in treatment decision-making, acute and long-term toxicities associated with various breast cancer therapies, and propose survivorship management plans in the introduction (page 3, line 52- 55). This review not only describes the toxicities of cancer therapy in the elderly, but also emphasizes the incorporation of geriatric assessment and patient preferences as the core of treatment decision-making, and recommends the monitoring and management of long-term toxicities in survivors. There is also a section on immunotherapy which was not present in the previous review.

" In this mini-review, we aim to provide a comprehensive overview of the current guideline recommendations for geriatric cancer patients in treatment decision-making, acute and long-term toxicities associated with various breast cancer therapies, and propose survivorship management plans."

(3) The Focus is Inconsistent
According to the introduction, the authors say they will focus the paper on "the unique challenges older breast cancer patients face in survivorship, focusing on treatment-related toxicities in breast cancer in this mini-review." My interpretation of this is that the authors will focus on discussing research that examines whether the complication rates from various breast cancer treatments differ among older patients versus younger patients. The authors do a really nice job of this in the paragraph covering lines 95-102: "A literature review on acute and late radiotherapy-related toxicity in older breast cancer 95 patients indicated that they tolerate radiotherapy as well as younger patients (14). Overall, acute 96 grade 3+ toxicity (0.0% - 10.5%) and late grade 3+ toxicity (0.0% - 13.0%) remained low. 97 Frequent late toxicities were ≤ grade 2, including subcutaneous fibrosis, breast deformity, and 98 telangiectasia. Grade 3 skin and subcutaneous toxicities were less than 5%. Grade 3 arm 99 lymphedema was 0.1% and ≤ grade 2 pulmonary toxicity rates were 0.4% and 0.1%, 100 respectively (14). Importantly, none of the studies that compared different age subgroups found 101 significant age-related differences in toxicity rates." This is a perfect example of how the paper should be focused – on describing whether older patients react differently than younger patients to each type of treatment. However, for some of the treatment options discussed in the review, the authors just summarize existing general evidence on complications from the treatment, and they do not mention whether these complication rates vary by age group. The focus of the paper is constantly switching back and forth. For example, in the "Surgery" section, the study

on axillary intervention that is discussed in the second paragraph (reference 7) uses a study sample of women 18 and over and does not discuss age subgroup analyses. If there is no existing research on this topic that compares complication rates among older versus younger patients, the authors should state this fact upfront, and then summarize the broad research for all age groups and hypothesize how the results might vary by age subgroup.

Reply: Thank you for the insight. We decided that the aim of this paper was to provide a comprehensive overview of the current guideline recommendations for geriatric cancer patients in treatment decision-making, acute and long-term toxicities associated with various breast cancer therapies, and propose survivorship management plans. We tried to gather age-specific data on the efficacy and toxicities of treatment, albeit finding a lack of data specific for the geriatric population in many of the trials. We found that age-specific data were best described for some treatment modalities, including CDK4/6 inhibitors and chemotherapy.

(4) Specific Edits
• Introduction: "Breast cancer, one of the most prevalent female cancers…" How prevalent? Cite statistics.

Reply: Thank you for the comment. We have added the statistics to the introduction (Page 2, line 39 - 40).

"Breast cancer is the most prevalent cancer among women worldwide, with an estimated 2.3 million new cancer cases (1 in 4 new cancer cases) in the year 2020 (1)."

• Introduction: I don't think you need to spend so much time defining the age cutoff for older adults. You chose 70, but then the studies that you cite and discuss throughout the paper use different definitions of older age (e.g., 65+), so there is no real reason for you to pick a cutoff in the beginning.

Reply: Thank you for the comment. We have omitted that in the new manuscript.

• Introduction: "This is associated with increased recurrence and decreased survival rates." Please provide a citation for this.

Reply: We have revised the introduction as suggested (page 2, 39 - 55).

"Breast cancer is the most prevalent cancer among women worldwide, with an estimated 2.3 million new cancer cases (1 in 4 new cancer cases) in the year 2020 (1). The median age of breast cancer diagnosis is 61, with 45% of breast cancer patients being over 65 years old and 10% are 80 or older at diagnosis (2). With an aging population, the number of geriatric breast cancer patients is expected to increase. Yet, data on the management of older cancer patients are scarce as most clinical trials have excluded or underrepresented older patients (3). Age-related variability in patterns of care is high and older patients frequently receive less aggressive treatment compared to their younger counterparts (2). Treatment decisions making should not be made based on chronological age alone, instead, they should involve comprehensive geriatric

assessments and consideration of functional age, estimated life expectancy, and patient preferences.

A previous review published in 2022 summarized the available data on treatment options, age-related factors, and toxicities pertinent to the management of older patients with breast cancer (4). In this mini-review, we aim to provide a comprehensive overview of the current guideline recommendations for geriatric cancer patients in treatment decision-making, acute and long-term toxicities associated with various breast cancer therapies, and propose survivorship management plans."

• Surgery: This second sentence seems to conflict with the third sentence. In the second sentence (discussing the reference 2 study), the authors say that the study found a low rate of systemic complications among women undergoing mastectomy or BCS, but then in the 4th sentence, when the authors are discussing the reference 5 study, that study found that mastectomy increased systemic complications. If these study results conflict with each other, the authors should discuss why this might be the case. Or at least, they should not say "in addition", but rather use a phrase such as, "on the contrary".

Reply: Thank you. We have revised this in the surgery section (Page 5, line 94 - 100)

"Breast cancer surgery is generally well tolerated in older patients. A prospective multi-center study in the UK of 2,816 women aged 70 and above who underwent mastectomy or breast-conserving surgery found that the overall rate of systemic complications including cardiorespiratory problems, stroke, deep vein thrombosis and pulmonary embolism was low (2.1%). The rate of local wound complications including hematoma, infections, and wound dehiscence was 18.4%. There were no deaths reported within 30 days of surgery or attributable to surgery (12). "

• Radiotherapy: This section would be more organized if the authors open the paragraph (2nd sentence) with listing the possible radiotherapy side effects (e.g., toxicity, lymphedema, cardiovascular events, etc.), and then proceed to discuss them in that order.

Reply: Thank you for the suggestion. We have added this to the radiotherapy section (page 8, line 172-173) "Late radiotherapy side effects include skin and subcutaneous toxicities, lymphedema, pulmonary and cardiac toxicities."

• Chemotherapy: "Studies have shown poorer cognitive function in patients treated with chemotherapy." Please cite (at least some) of these studies.

Reply: Thank you. We have included a systematic review and metaanalysis that studied the cognitive impairment following chemotherapy (page 10, line 228 - 234).

"Chemotherapy-induced cognitive impairment may lead to poorer quality of life and loss of independence in elderly patients. A systematic review and meta-analysis of 52 studies showed that the prevalence of cognitive impairment following chemotherapy for breast cancer were 21-34% assessed by neuropsychological tests, 44% by self-

report, and 16% by short cognitive screening tools (32).

• Immunotherapy: In lines 205-206, the authors write that similar rates of immune-mediated adverse events of any grade were observed in the experimental and placebo arms (43.6% vs. 21.9%). I would not consider 43.6% and 21.9% to be similar rates.

Reply: thank you for the comment. We have revised the immunotherapy section (page 10 - 11, line 236-263) and the previous study is no longer included for better clarity and flow of the paper.

• Target Therapy: "Cumulative dose of anthracycline chemotherapy, underlying cardiovascular disease, prior radiation to the heart, and old age were significant risk factors (27)." Should be change to: "Cumulative dose of anthracycline chemotherapy, underlying cardiovascular disease, prior radiation to the heart, and old age have been found to be significant risk factors (27)."

Reply: This has been rephrased as suggested to "Cumulative doses of anthracycline chemotherapy, underlying cardiovascular disease, prior radiation to the heart, and old age have been found to be significant risk factors of anti-HER2 targeted therapy induced cardiotoxicity. " (Page 12, line 272 - 274).

• Conclusion: Could use further summary of the overall findings of the review. For example, overall, do older patients, as compared to younger patients, have more adverse outcomes from various treatments? If so which ones? Which treatment options did not have any research comparing results by age group? Summarize the overall findings in the first paragraph of the conclusion.

Reply: Thank you for your kind suggestion. We have revised the conclusion on page 12 - 13, line 282 - 292.

"Older patients with breast cancer are a unique group of patients with specific needs and treatment considerations. The diversity of functional health, comorbidities, treatment priorities and preferences among older patients necessitates use of comprehensive geriatric assessment to assist physicians in tailoring treatment plans to meet each individual needs. It is important for physicians to carefully consider age-specific treatment efficacy and potential treatment-induced toxicities when making treatment decisions. Breast cancer surgeries were generally well tolerated. No significant age-specific differences were observed in radiotherapy-induced toxicities. It should be noted that older patients were more likely to suffer from grade 4 hematological toxicity when treated with CDK4/6 inhibitors or chemotherapy. Older patients remain significantly under-represented and understudied in many major clinical trials. Further efforts to enhance the representation of older patients in breast cancer trials are warranted."