

Peer Review File

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Reviewer A

This paper represents a systematic review of available literature regarding treatment of older adults with combination chemotherapy. 5 studies were identified and reviewed. Overall, this represents an interesting and common clinical scenario, however, the limited available literature and the quality of the included studies limits the impact of the review. Addressing the following comments would strengthen the manuscript:

Comment 1: I recommend including a summary of the results in the abstract.

Reply 1: Thank you for this suggestion, changes in the text below.

Changes in the text: We have added results to the abstract as advised. Page 2, Lines 39-42

Comment 2: Please elaborate on why 4 studies were excluded for the "wrong" study design.

Reply 2: These four studies were excluded given the following reasons related to the study design itself:

Effect of advanced age, elevated bilirubin, and disease extent on outcomes of unresectable pancreatic cancer (UPC) patients receiving first-line chemotherapy: A population-based study. (Cherniwasky, 2017) The abstract for this study does not specify if there were two separate groups of age for the reported results. Since there is not clear comparison between the two groups and only 55% of the population was >70 years, this study design did not meet criteria for our systematic review.

Gemcitabine + nab-paclitaxel as first-line chemotherapy for Japanese patients with advanced pancreatic cancer in real-world clinical practice: A retrospective study. (Yamaguchi 2016) Age range does not meet criteria (47-79), not enough information about potential subgroups that could qualify for our inclusion criteria

FOLFIRINOX therapy in the elderly patients with unresectable pancreatic cancer (Ishii, 2016) There was insufficient data to support the result that there was a significant difference in the response rate of the two groups.

Combination therapy versus gemcitabine monotherapy in the treatment of elderly pancreatic cancer: a meta-analysis of randomized controlled trials (Jin, 2018) Meta-analyses were not included in our analysis since systematic reviews are based on original research articles and hence this is considered as secondary sources.

Changes in the text: We specified why these studies were excluded on Pg. 6 Lines 146-147. We also modified Table 1 to add meta-analyses as part of the exclusion criteria since these were not included in our review.

Comment 3: The conclusion of the first study reviewed was that FOLFIRINOX is feasible

and effective in "selected, fit older adult patients." What demographic and clinical data including comorbidities and functional status were reported in the paper to justify this conclusion?

Reply 3: The population in this study had the following characteristics: Performance Status (0=15%, 1=24%, 2=3%), BMI (Median 24, Range 18-32), concurrent medications (<=3, 24 and >=3, 16). Also, Charlson Comorbidity Index at the time of diagnosis: Median 10, Range 9-12. Diabetes and hypertension were also included in the univariate analyses.

Changes in the text: We summarize this study's population on Pg. 6-7 Lines 155-159

Comment 4: Pg 10, line 206 says no deaths due to toxicity were reported. Is this just in the abstracts that were excluded? It appears so, since one death was reported in two studies per the discussion, pg 11 line 244. Please clarify.

Reply 4: This statement refers to the abstracts alone, but we did modify it in the text because we went back through all the abstracts on Table 3 and there was one reported death related to treatment, attributed to septic shock (Baldini et al 2015, Abstract #3 on Abstract's table)

Changes in the text: We added a statement about this one death reported in this abstract on Pg. 10 Line 236-237 and clarified that this information refers to the abstracts alone.

Comment 5: Please add to the discussion

- a) How duration of treatment and tolerance of treatment is influenced by patient age.
- b) The fact that most of the referenced studies explored FOLFIRINOX, but most older patients are treated with gem/abraxane. Should more FOLFIRINOX be used?
- c) expand on clinical utility of these findings

Reply 5: When compared to younger populations, older adults who benefit from combination chemotherapy benefit for similar durations to that seen in younger adults. Rates of neutropenia appear higher, but other toxicities similar to that seen with younger adults. These findings suggest that comorbidity rather than age should determine whether older adults receive combination chemotherapy for advanced pancreatic cancer. Direct comparisons between regimens has not been performed and escapes the scope of this systematic review. Therefore, we can not suggest that more FOLFIRINOX be utilized. Physicians may use this information to inform treatment recommendations, stipulating that age alone should not be the criteria for selecting a chemotherapy regimen.

Changes in the text: Please see Pg. 12 Line 282-285.

Comment 6: The conclusion that combination chemotherapy is safe and "effective" for older adults should be softened. This is only based on the available literature which is rather sparse. Also, stating that these patients should be included in interventional clinical trials is outside the scope of this review and should also be softened.

Reply 6: Please see changes as referenced below

Changes in the text: We adjusted the text as suggested in the abstract Pg. 3 Line 50 and main text Pg 13 Lines 308-314

Comment 7: How many case series were excluded? It seems that given only 5 studies eligible based on the criteria, case series examining this question should be included.

Reply 7: Our initial search of 1479 studies included 17 case series, 16 of which were excluded due to: not related to pancreatic adenocarcinoma but other GI tumors, and included other chemotherapy regimens or chemotherapy complications that were outside the scope of this study. One case series was on metastatic adenocarcinoma, but its focus was not related to our main search and did not reference the older adult population. (*Bachet, 2009. Second- and third-line chemotherapy in patients with metastatic pancreatic adenocarcinoma: Feasibility and potential benefits in a retrospective series of 117 patients*)

Changes in the text: No changes were made in the text

Comment 8: Did 15 abstracts not get published as manuscripts or did the authors not have access to the full texts?

Reply 8: The 15 abstracts reported were not published as manuscripts. They were either part of conferences or abstracts presentations alone.

Changes in the text: We clarified this on Pg. 10 Line 233.

Reviewer B

This systematic review article includes five studies that assess the survival outcomes and adverse events in patients 65 years and older diagnosed with pancreatic cancer and treated with combination chemotherapy.

Comment 9: It would be interesting if the authors could abstract the outcomes data on patients between 65-75 in the PRODIGE and >65 in MPACT study. As mentioned in the paper, the PRODIGE only excluded patients above 75, and MPACT had 42% of the population considered elderly.

Reply 9: We appreciate this comment. Unfortunately, neither study presents subgroup analyses by age or provide specific information regarding this age groups. They do, however, make general statements about age that we will include in our manuscript.

PRODIGE: We reviewed the supplementary appendix for the Conroy et al PRODIGE study (2011)¹ and they stated that age >65 years old was identified as an independent adverse prognostic factor for overall survival (HR 1.47; 95% CI, 1.07 to 2.02 p=0.019) but there is not further information about this on the manuscript or the supplementary materials. In 2018, Conroy et al published the PRODIGE study on FOLFIRINOX vs. Gemcitabine as adjuvant therapy for early stage pancreatic cancer. In the univariate analysis published on the supplementary materials of the PRODIGE study (2018)², Table S4 shows that there was no statistically significant difference between the <70 yo group and the >=70 yo group (Hazard ratio 1.16; 95% CI 0.89-1.52 p=0.28) in overall survival.

¹ Conroy T, Desseige F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-25

² Conroy T, Hammel P, Hebbar M, et al FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018;379:2395-406. DOI: 10.1056/NEJMoa1809775

MPACT: Multivariable analysis showed that age was one of the statistically significant independent predictors of survival when comparing age <65 vs. ≥65 (HR 0.81; 95%CI 0.69-0.96, p=0.16)

Changes in the text: This information was added to the text on Pg. 10-11 Line 243-259, and a reference for the 2018 PRODIGE publication added.

Comment 10: As mentioned in the limitation section, the sample size of the studies included was small. For instance, in the first study, the authors showed that the decrease in overall survival was not statistically significant when a dose attenuation was required (11.7 vs. 16.6 months). Nonetheless, this difference might be clinically relevant with a difference of about five months, resulting almost in a 30-40% decrease in survival. The lack of statistical significance is most likely due to the small sample size. The authors conclude that the combination therapy is feasible and safe, but all the studies presented suggest significant toxicity. For instance, in the first study, dose attenuation was required in more than half of the patients. Is that an acceptable percentage in the authors' opinion?

Reply 10: We thank the reviewer for this thoughtful comment. We agree that dose attenuations were notable in the older adult population and have addressed this in the text.

Changes in the text: We mention this in our text on Pg. 12 Line 287-290.