Peer Review File

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Review Comments

The authors reviewed the role of biomarkers in the assessment of response to neoadjuvant therapy in pancreatic cancer and the assessment tools. However, it is noted that the authors only reviewed several of the more promising biomarkers and neglected others. Moreover, there are also some confusing information in the manuscript.

Following are some suggestions to improve the article.

Comment 1: Title

(1) In the title, please clearly identify this manuscript as a Narrative Review. E.g. "Measuring Response to Neoadjuvant Therapy in Pancreatic Cancer: A Narrative Review".
Reply 1: We have added “Narrative Review” to the title
Changes in text: Measuring Response to Neoadjuvant Therapy using Biomarkers in Pancreatic Cancer: A Narrative Review

(2) I suggest the authors specify "Biomarkers" in the title.
Reply 2: We have added Biomarkers to the title
Changes in text: Measuring Response to Neoadjuvant Therapy using Biomarkers in Pancreatic Cancer: A Narrative Review

Comment 2: Abstract

It is a great pleasure to see that the authors have been described the objective, background, methods, discussion, and conclusion in the Abstract (lines 13-29). However, there are still some issues that needs to be addressed. (1) Please combine "Background" and "Objective" into a subsection entitled "Background and Objective", and revise the name of the subsection "Discussion" to "Key Content and Findings".

Reply 1: We have combined Background and Objective and revised the name of the subsection “Discussion” to "Key Content and Findings".

(2) In the "Methods" section of the Abstract (lines 19-21), we suggest the authors also specify the timeframe (e.g. "January 1, 2011 to December 31, 2022") and the language for these included article (e.g. "publications in English").

Reply 2: We have specified the timeframe
Changes in text: This literature review included publications in English written between January 1, 2011 to March 31, 2022.

(3) The abstract should not contain any citations, e.g., "the last 20 years.1" (line 17).

Reply 3: We have removed citations from the abstract.

Comment 3: Keywords

Line 30: would "pancreatic cancer" be more appropriate than "pancreas"? Reply: We have changed the word to pancreatic cancer from pancreas.

Comment 4: Introduction

Lines 44-45: "This review highlights the role of biomarkers in evaluating response to neoadjuvant treatment in pancreatic cancer". We suggest the authors could give a brief background on "biomarkers" and cite relevant studies in this field to explain the reason for "highlights the role of biomarkers".

Reply: We have included brief additional information on biomarkers to explain the reason for highlighting the role of biomarkers.

Changes in text: A biomarker is defined by the NIH Biomarker Working Group as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to therapeutic intervention”.[1] To date the most used biomarker in the detection and management of pancreatic cancer is Carbohydrate Antigen 19-9 (CA 19-9), however it is limited in its utility. Thus multiple studies are ongoing to improve diagnosis and guide management PDAC.[1-3]

Comment 5: Methods

It’s great that the authors provide the information of the searches in the Methods (lines 51-59). Only one minor issue, the two places have different timeframe: "2011-2022" (line 55) and 2012-2022 (table 1). Please re-check and revise it.

Reply: We have changed the table to reflect the appropriate time frame of 2011-2022

Comment 6: Narrative

(1) For a clearer article structure, we strongly suggest the author number the subheadings. Reply 1: We have numbered the subheadings.

(2) We suggest that the authors could add a short paragraph about "Serum Biomarkers"before the subsection "Carbohydrate Antigen 19-9 (CA 19-9)". Also, this sentence"Several serum biomarkers have been investigated in their utility in determining response to neoadjuvant therapy" (Lines 63-64) could be moved to this paragraph.

Reply (2): We have added a short paragraph to introduce the topic of serum biomarkers.
Changes in Text: Several serum biomarkers have been investigated in their utility in determining response to neoadjuvant therapy. The most studied and only FDA approved serum biomarker is CA 19-9, however many other serum biomarkers are currently under investigation.[3] Other serum biomarkers include Carcinoembryonic antigen (CEA), circulating tumor DNA (ctDNA) and circulating tumor cells (CTC).[4]
(3) Line 77: please add the unit "91.8 U/ml".
Reply 3: We have added the Unit 91.8 U/ml

(4) Please cite the reference for this sentence: "In a systematic review of the prognostic value of CA 19-9 after NAT for PDAC, Ye et al found ..." (Line 78). Also, suggest put citation after “et al.”, e.g., line 93 ("Truty et al [12] conducted ..."), line 142, etc. Pleasecheck the entire manuscript to address similar concerns.

Reply 4: we have cited the reference: "In a systematic review of the prognostic value of CA 19-9 after NAT for PDAC, Ye et al found ..." (Line 78). We have changed all citations that include “et al” to include the citation immediately after it.

(5) Serum Biomarkers: The authors only reviewed CA 19-9 and ctDNA in "Serum Biomarkers", what about CEA, CTC and others? The authors could consider a brief review of these in the subsection "Others".

Reply 5: We have included another subsection titled “Other Serum Biomarkers” in which we review CEA, CA- 125, CTC.

Changes in text: Other serum biomarkers have been studied for their use in evaluating pathologic response to NAT for PDAC. Carcinoembryonic antigen (CEA) is commonly used in colorectal cancer and has been noted to be elevated in more than 60% of patients with PDAC, however it has low diagnostic sensitivity for the disease and thus is not commonly used. [24] Recently, in a retrospective review of 319 patients with localized PDAC, Kato et al [25] found that high CEA level pre-neoadjuvant chemoradiation was the most significant independent predictor of poor post-surgical disease free and overall survival. While CEA may not be useful as a diagnostic biomarker in PDAC, it could prove more useful as a prognostic or predictive biomarker in patients undergoing NAT.

Cancer antigen 125 (CA-125) has also been evaluated as diagnostic and prognostic biomarker in PDAC. It has a lower sensitivity than CA 19-9 and while it can be followed if high at baseline diagnosis, it has not proven to be as useful as other biomarkers.[8]

Circulating tumor cells (CTC) are tumor cells that enter the peripheral circulation and are thought to ultimately play a role in metastatic disease.[11] In a meta-analysis of 19 studies, with over 1300 patients with pancreatic cancer, Wang et al [26] found that patients with detectable CTC (CTC positive) had worse overall and disease-free survival than those without detectable CTC. Additionally, they found that in patients of Asian and Western ethnicity who were CTC positive had significantly shorter overall survival.[26] Martini et al [27] similarly found worse overall survival for patients with detectable CTC at diagnosis. While CTC appears to be a useful prognostic biomarker, larger scale studies are needed to improve CTC isolation techniques and to further assess utility as a therapeutic predictive biomarker.[27]