Peer Review File

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Reviewer A

This article review reviews the treatment of metastatic RCC on precision medicine. However, there are some issues that need to be addressed. Please see the comments below.

Main consideration

Comment 1: Introduction

(1) Before presenting the treatment of mRCC, we suggest the authors could give a brief description of the mRCC disease so that the reader can understand why it should be taken seriously.
Ans. We are sorry for forgetting a brief description of the mRCC disease

In 2020, new cases of renal cell carcinoma (RCC) were diagnosed about 430,000 patients all over the world (1). Clinically, surgery is the first choice for RCC without metastasis. In addition, approximately 30% of new RCC cases are metastatic RCC (mRCC), and these patients mainly receives systematic therapy (2). (Line42-45)

(2) Given that there are many similar reviews in this field (PMID: 35531636, 35385828), what does this review add to existing knowledge? How does this review differ from previous reviews? Please clearly state this.
Ans. Thank you for the precious comment. We added the following sentences as introduction.

The difference between our narrative and other reviews discussed we reported not only untreated clear cell mRCC but also untreated non-clear cell mRCC (12,13).
(Line69-70)

(3) Lines 57-58: "In this review, we discuss the optimal treatment modality for patients with mRCC based on the currently under developed drugs and their issues". Could you be more clear? How did the author determine the best method? How should the reader interpret and use the results?
Ans. Thank you for the precious comment. We added the following sentences as introduction.

using analysis of polybromo 1 (PBRM1), BRCA1-associated protein 1 (BAP1), plasma cell-free DNAs (cfDNA), repertoire analysis of T-cell receptors, the gut microbiome and so on.
(Line72-73)

Comment 2: Methods

(1) We suggest the authors add more detailed information, including date of search, timeframe, inclusion and exclusion criteria, and selection process.
Ans. Thank you for the precious comment. We added your comments.

A literature search was performed on PubMed for articles published from January 2008 to December 2022, focusing on articles relevant to mRCC and first line mRCC therapy using IO

drugs. (Line79-80)

(2) To further make the information more easy-going and self-explaining, please also include a completed table (https://amj.amegroups.com/pages/view/guidelines-for-authors , content 2.2.3 Narrative Review (Also Called Literature Review)--Table X) in the Methods, which includes an independent supplement table to present detailed search strategy of one database as an example. Here are two examples for your reference:
https://atm.amegroups.com/article/view/91685/html (See Table 1-2)
https://atm.amegroups.com/article/view/91974/html (See Table 1)
This part is essential as it reflects the sources of evidence (even though it is not a systematic review). This is to transparently report the process, not to judge it.
Ans. Thank you for the precious comment. We added your comments.

The keywords, "mRCC," "gene expression," and "precision medicine" from clinical studies were used (Table 1). (Line81-82)

Comment 3: Main Body
(1) e.g., "OS improvement" (line 78), "a significantly longer PFS" (line 112), etc.
(2) The prognosis is influenced by several factors, including tumour size, degree of invasion and metastasis, histologic type, and nuclear grade. The 2004 World Health Organization (WHO) classification of genitourinary tumours recognizes over 40 subtypes of renal neoplasms. Could the authors discuss it in more detail (or briefly discuss the four major histologic subtypes)?
Ans. Thank you for the precious comment. We added your comments.

The difference between our narrative and other reviews discussed we reported not only untreated clear cell mRCC but also untreated non-clear cell mRCC (12,13).
(Line69-70)

CheckMate 214, comparing nivolumab + ipilimumab versus sunitinib.
(Line98-108)
Nivolumab + cabozantinib had significant benefits over sunitinib with respect to PFS.
(Line120-122) (Line124-127)

In a CLEAR trial comparing pembrolizumab + lenvatinib or sunitinib to advanced RCC.
(Line139-140) (Line142-144)

In a JAVELIN Renal 101 clinical trial comparing avelumab + axitinib or sunitinib for patients with mRCC.
(Line149-152)

In an IMmotion151 trial, atezolizumab + bevacizumab or sunitinib was compared as first line treatment for treatment-naïve patients with mRCC.
(Line157)

For these reasons, therapeutic efficacy for mRCC has dramatically improved (41). The combination therapy of nivolumab + ipilimumab or pembrolizumab + lenvatinib may be the good option for IMDC poor risk group;
(Line164-166)

(2) To better help readers understand the "optimal treatment modality for patients with mRCC", could the authors refine Figure 1 to summarize the factors that influence treatment considerations for individual patients (which could include histopathology, biomarkers, etc.)?
Ans. Thank you for the precious comment. We are the correction Figure 1.

(3) It is necessary and important to transparently discuss the review's LIMITATIONS. A separate paragraph is highly suggested.
Ans. Thank you for the precious comment.

The limitation of our narrative review is no consensus on the optimal treatment for such patients because there are no phase III clinical studies based on biomarkers for mRCC treatment. In the near future, we believe that these biomarkers will lead to precision medicine in the treatment of mRCC by being analyzed carefully and strategically.
(Line272-275)

Minor suggestions
Comment 4: Abstract
The abstract is not informative enough.
(1) In the "Methods" section of the Abstract (lines 27-28), we suggest the authors also specify the timeframe and the language for the included article (e.g. "publications in English").
Ans. Thank you for the precious comment. We added Table 1.

(2) To better focus on the main conclusions and how the review may potentially impact future researches, clinical practice and policy making, could the authors refine the "Conclusions" (lines 34-35)?
Ans. Thank you for the precious comment.

Especially, the gut microbiome appears to be an importance factor to treatment of cancer.
(Line35-36)

This revision may further specify the contribution of this review.

Comment 5: Keywords
We suggest replacing the term "renal cell carcinoma" with "metastatic renal cell carcinoma".
Ans. Thank you for the comment. We corrected the term.

Comment 6: Others
(1) Please define all abbreviations mentioned for the first time both in the text, table footnotes and

figure legend, such as VEGFR (figure 1), VEGFR (table 2). Please check the entire manuscript to address similar concerns.
Ans. Thank you for the comment. We corrected the terms.

(2) It is "narrative review" not "narrow review" (line 21). In addition, please also add a statement "We present the following article in accordance with the narrative review reporting checklist" at the end of the Introduction.
Ans. Thank you for the comment. We corrected the terms and added your comments at the end of the Introduction.

Comment 7: Format
Due to the recent editorial update on the regulations of manuscripts, we hope authors use a structured introduction to increase readability: a) Background, b) Rationale and knowledge gap, c) Objective.
The authors may refer to the Structure template (https://cdn.amegroups.cn/static/public/2.2.3-Structure%20of%20Narrative%20Reviews-template-V2022.11.4.docx).
Ans. Thank you for the comment. We use a structured introduction to increase readability.

Reviewer B
Sugimoto et al. report a narrative review examining treatment strategies in metastatic RCC with a focus on precision medicine, specifically investigating biomarkers for therapy responsiveness in mRCC. While this is undoubtedly a relevant question, and there is utility in collating the material together, it should be noted that the content of this review heavily overlaps with other recently publishing reviews (Pubmed IDs including 34265458, 35385828). The content is also well-documented in relevant national and international treatment guidelines - for example, https://www.annalsofoncology.org/article/S0923-7534(19)31157-3/fulltext - this is particularly relevant for the first part of the results that is really just a description of the relevant large phase 3 trials. It would be informative for the authors to clarify how their review differs from/provides additional information to these existing reviews.
Ans. Thank you for the precious comment. We added your comments.

The difference between our narrative and other reviews discussed we reported not only untreated clear cell mRCC but also untreated non-clear cell mRCC (12,13).
(Line69-70)

It is also preferred that other related reviews are cited. I would potentially suggest the authors focus more on the “precision medicine” angle, rather than re-iterating well-reviewed topics. The authors do not seem to really integrate the material together as would be preferred in a narrative review – it is more of a study-by-study description of specific findings, it is not entirely clear why the authors pick some studies over others. As a general point, the authors are not clearly specifying which histological subtype of RCC is included in each trial, this is highly relevant. The majority of trials here related to clear cell subtype.

Ans. Thank you for the precious comment.

1. We are also discussed to treat for non-clear cell RCC.

CheckMate 214, comparing nivolumab + ipilimumab versus sunitinib.
(Line98-108)
Nivolumab + cabozantinib had significant benefits over sunitinib with respect to PFS.
(Line120-122) (Line124-127)

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For these reasons, therapeutic efficacy for mRCC has dramatically improved (41). The combination therapy of nivolumab + ipilimumab or pembrolizumab + lenvatinib may be the good option for IMDC poor risk group;
(Line164-166)

2. *We are also discussed the biomarkers to treat mRCC.*

Recently, many DNA-based biomarkers such as tumor mutational burden (TMB), tumor indel burden (TIB), human leukocyte antigen (HLA) have been associated with response to immune checkpoint inhibitors (ICI). Biomarker analysis of CheckMate214 showed that low TIB was associated with PFS, but not OS (42). (Line170-173)

Specific comments:
Line 136-138 - the authors seem to jump between discussion of gene expression and mutational biomarkers, these should really be discussed separately, as they are measuring something fundamentally different
Ans. Thank you for the comment. We discussed only mutational biomarkers.

Mutational biomarkers reported
(Line 183)