



OPEN ACCESS

EDITED AND REVIEWED BY
Ronald M Bukowski,
Cleveland Clinic, United States

*CORRESPONDENCE
Maria Giuseppa Vitale
✉ vitalemariag@gmail.com

SPECIALTY SECTION
This article was submitted to
Genitourinary Oncology,
a section of the journal
Frontiers in Oncology

RECEIVED 10 March 2023
ACCEPTED 13 March 2023
PUBLISHED 20 March 2023

CITATION
Vitale MG, Maruzzo M and Sabbatini R
(2023) Editorial: The ever-changing
scenario of first line treatment of
metastatic renal cell carcinoma.
Front. Oncol. 13:1183749.
doi: 10.3389/fonc.2023.1183749

COPYRIGHT
© 2023 Vitale, Maruzzo and Sabbatini. This is
an open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that
the original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution or
reproduction is permitted which does not
comply with these terms.

Editorial: The ever-changing scenario of first line treatment of metastatic renal cell carcinoma

Maria Giuseppa Vitale^{1*}, Marco Maruzzo²
and Roberto Sabbatini¹

¹Medical Oncology, Department of Oncology and Haematology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, ²Medical Oncology Unit 1, Department of Oncology, Istituto Oncologico Veneto IOV-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy

KEYWORDS

renal cancer, first line treatment, combination therapy, prognosis, nephrectomy

Editorial on the Research Topic

The ever-changing scenario of first line treatment of metastatic renal cell carcinoma

Renal cell carcinoma (RCC) accounts for 4.1% of all new cancers, with a median age at diagnosis of 64 years. Approximately 85% of kidney tumors are RCC (renal cell carcinoma), and 70% of these have a clear cell histology (ccRCC) (1–4).

For selected patients with limited disease, partial nephrectomy (PN) is an option to treat RCC with oncological outcome comparable to radical nephrectomy. In their meta-analysis, Bai et al. investigated the effect of positive surgical margins (PSM) in term of prognosis. The pooled results showed a significant impact of PSM during PN in term of risk of recurrence (odd ratio, OR 3.93) and risk of metastasis (OR 4.63). However, PSM did not affect the risk of all-causes or cancer-specific death. Therefore, the study supports close monitoring for patients with PSM after PN.

From a surgical perspective, tumor thrombus (TT) is often associated to primary RCC. In a mono-institutional cohort, Wang et al. analysed the impact in survival of different histologies (clear and non-clear cell) in RCC with TT. The presence of thrombosis was more common in papillary RCC (pRCC); the oncological outcomes (both progression-free and overall survival) were worse for this subgroup of patients. Moreover, histology is independently associated to worst OS and PFS and strict follow-up should be followed for pRCC patients with TT.

Tyrosine kinase inhibitors (TKIs) such as Sunitinib or Pazopanib have been widely used in first-line treatment. Immunotherapy has provided a revolution in treatment options and recently, combination therapy ICI (Immune checkpoint inhibitors) -TKI and ICI-ICI have demonstrated remarkable efficacy in patients with mRCC. Tumour histology and risk stratification of patients is important in therapy selection.

In the paper by Dong et al., the authors investigated the expression profile of TFE3 of in 796 patients with RCC and the clinicopathological features as well as prognosis of TFE3-positive RCC. 91 (91/796, 11.4%) patients were TFE3 positivity expression and only 31 (31/91, 34.1%) of the patients were diagnosed with Xp11.2 translocation RCC. In this study, nuclear TFE3 expression is not specific to the Xp11.2 translocation RCC. Moreover, the

positive TFE3 expression is associated with tumour progression and poor prognosis in patients with RCC irrespective of the presence of TFE3 translocation.

In the paper by [Qin et al.](#), they conducted a Bayesian network meta-regression analysis to provide a head-to-head comparison of first line therapeutic immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitor (TKI) combinations for metastatic renal cell carcinoma. After analysing a total of 22 randomised clinical trials (RCTs) the combination Lenvatinib-Pembrolizumab shows dominance of progression free survival (PFS) and Pembrolizumab-Axitinib shows superiority in overall survival (OS). After meta-regression analysis, for hazard ratio (HR) of PFS, Lenvatinib-Pembrolizumab shows advantages; for HRs of OS, Pembrolizumab-Axitinib demonstrates superiority; for objective response rate (ORR), Lenvatinib-Pembrolizumab provides better results. About tolerability, the combination Atezolizumab-Bevacizumab is better. The authors conclude that Pembrolizumab-Axitinib should be recommended as the optimal therapy for the first line treatment of mRCC thanks to the lower toxicity and the higher quality of life.

Although the adverse events of both drug classes of combination therapy are now well-known, it may be difficult to recognise which drug is related to a particular adverse event. [Boutros et al.](#) reported two cases of patients with muscle enzyme elevation in association with hypothyroidism during treatment with Pembrolizumab-Axitinib for mRCC. The myopathy rapidly resolved after hormone replacement therapy with levothyroxine. This adverse event is rare and in the differential diagnosis with immune-related myositis which has different pathogenesis and course.

In a changing scenario with new multiple combinations of drugs effective for RCC, other mechanisms of action are desirable. [Wang et al.](#) the role of Glutamate dehydrogenase 1 (GLUD1), which plays a critical role in the malignancy of diverse tumors. They found that GLUD1 has a novel tumor-suppressing role of GLUD1 in ccRCC, different from that in other tumors, and these results

provide a theoretical basis for GLUD1 as a therapeutic target and prognostic marker in renal cancer.

In summary, in the ever-changing scenario of first line treatment for RCC, this collection highlights the significance of appropriate surgery and pathological reports, to ensure adequate follow-up to patients with a greater risk of relapse. Moreover, it is of crucial significance the appropriate choice of the first line therapy among all the different approved treatments, to maximise patients' benefit. Finally, identifying biomarkers or possible targets for new drugs development is critical to find out treatment strategies for RCC patients.

Author contributions

MV, MM, RS drafted, reviewed, edited, finalized the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. SEER Cancer Stat Facts. *Kidney and renal pelvis cancer*. Bethesda, MD: National Cancer Institute. Available at: <http://seer.cancer.gov/statfacts/html/kidrp.html>. Accessed March 6, 2023.
2. Moch H, Gasser T, Amin MB, Torhorst J, Sauter G, Mihatsch MJ. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: A Swiss experience with 588 tumors. *Cancer* (2000) 89:604–14. doi: 10.1002/1097-0142(20000801)89:3<604::AID-CNCR16>3.0.CO;2-Q
3. Leibovich BC, Lohse CM, Crispen PL, Boorjian SA, Thompson RH, Blute ML, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. *J Urol* (2010) 183:1309–15. doi: 10.1016/j.juro.2009.12.035
4. Lipworth L, Morgans AK, Edwards TL, Barocas DA, Chang SS, Herrell SD, et al. Renal cell cancer histological subtype distribution differs by race and sex. *BJU Int* (2016) 117:260–5. doi: 10.1111/bju.12950