Systematic Review to Summarize Treatment Patterns, Guidelines, and Characteristics of Patients With Renal Cell Carcinoma (RCC) in Asia-Pacific (APAC)

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BACKGROUND

- Kidney cancer has a major impact in APAC. Although the incidence was lower in this region than North America and Europe combined in 2020 (36% [n = 156,470] vs. 50% [n = 215,586], respectively), mortality was higher (45% [n = 80,251] vs. 40% [n = 70,845]).[1]
- RCC accounts for ~85% of all kidney cancers; this includes clear cell (cc; ~75–80%), papillary (~10–15%), and chromophobe (~5%) subtypes.[2,3] Advanced/metastatic RCC has a poor prognosis, with a 5-year survival of only 16%.[4]
- Management options for advanced/metastatic RCC are evolving to improve this situation. Immunotherapy combinations have been shown to increase survival versus sunitinib (a tyrosine kinase inhibitor [TKI]) in patients with ccRCC enrolled in the Keynote 426, Keynote 581/CLEAR, CheckMate 214, and Checkmate 9ER studies.[5–8]
- As a result, immunotherapy-based regimens are now recommended as first-line (1L) systemic therapy for advanced/metastatic ccRCC in US and EU guidelines.[9,10] There are more limited treatment options in the adjuvant setting, although an interim analysis of Keynote 564 demonstrated that pembrolizumab may provide significant improvement in disease-free survival compared to placebo after surgery in patients who were at high risk for recurrence.[11]
- Unfortunately, there are few studies that have examined the treatment landscape in advanced/metastatic or adjuvant RCC in APAC in detail, including the impact of the latest guideline recommendations.

OBJECTIVE

- This systematic review was conducted to determine patient characteristics, treatment patterns, and guidelines in advanced/metastatic and adjuvant RCC of any cause in APAC.

METHODS

- Embase®, MEDLINE® (via PubMed®), and relevant congresses were searched for RCC records in accordance with PRISMA guidance.[12] The inclusion criteria are summarized in **Table 1**. Quality assessment was based on the Downs and Black checklist.[13]

Table 1. Eligibility Criteria for Study Inclusion

Parameter	Inclusion criteria
Population	Patients with adjuvant, advanced/metastatic, or von Hippel Lindau disease–associated RCC
Intervention	Systemic therapy (surgical, ablative, neoadjuvant interventions were excluded)
Comparators	Not applicable—noncomparative studies
Outcomes/settings	Treatment patterns, patient characteristics, adjuvant therapy
Time	January 2016 to March 2021 (January 2019 to March 2021 for congresses)
Study design	Observational studies, clinical practice guidelines/algorithms (national and regional), and consensus statements published in English. Reviews of guidelines were excluded

RESULTS

Population

- 1,008 records were identified; 9 studies and 3 clinical practice guidelines/consensus statements were included.

Patient characteristics

- Patient characteristics are shown in **Table 2**.[14–17] Due to variations in clinical setting and reporting, no clear trends in clinical characteristics and prior treatments were observed. However, there was a higher prevalence of males with RCC.
- Recurrence rate after nephrectomy was 47% in 1 study, highlighting a relatively high recurrence rate.[16]

Treatment patterns

- Seven studies reported treatment patterns (**Table 3** and **Table 4**).[15–21] Five studies were in advanced/metastatic RCC and included 1L (n = 5), second-line (2L; n = 5), and third-line (3L; n = 2) therapies, and 2 studies were in adjuvant RCC.
- In advanced/metastatic RCC, the most common class of 1L therapy was TKIs, with sunitinib being the most used (33–100%). The most used 2L treatments were everolimus, a mechanistic target of rapamycin kinase inhibitor (mTORi; 13–85%), and axitinib, a TKI (2–89%).

- In adjuvant RCC, sunitinib was the most used treatment (54%) followed by mTORis (27%) with immunotherapy being less commonly used (16%) in 1 study.[16]

Table 2. Data on Clinical Characteristics, Prior Treatments, and Recurrence[a]

Study	Design	N	Population	Age, Years	Male, %	Risk Factors, %	Subtype, %	Prior Surgery/Recurrence, %
Ray 2016[14] (India)	Retrospective	75	Surgically treated RCC	53 (mean)	68	Tobacco use: 60[b] Hypertension: 41 Occupational: 5	Clear: 89 Papillary: 5 Chromophobe: 1 Sarcoma: 3 Poorly differentiated: 1	Nephrectomy: 99
Ramaswamy 2017[15] (India)	Prospective	212	Metastatic RCC	56 (median)	78	NR	Clear: 68 Papillary: 12 Chromophobe: 2 Sarcomatoid: 3 Other/unavailable: 15	Nephrectomy: 55
Tiwari 2018[16] (India)	Retrospective	292	Postoperative recurrence in RCC	50 (median)	76	NR	Clear: 71 Nonclear: 29	Nephrectomy: 100 Recurrence: 47 5-year recurrence: 18
Hinata 2020[17] (Japan)	Retrospective	208	Previously treated metastatic RCC	67 (mean)	76	NR	Clear: 77 Nonclear: 23	Nephrectomy: 83

[a]Data from largest studies with sex and age recorded are shown; [b]N = 55/75 patients with risk factors reported. NR = not reported.

Table 3. Treatment Pattern Studies in the Advanced/Metastatic Setting

Study (Country)	Settings/N	1L, %	2L, %	3L, %	Adjuvant, %
Zanwar 2016[18] (India)	Advanced/metastatic RCC (palliative) N = 46	Sorafenib: 41 Sunitinib: 33 Pazopanib: 20 Other: 7	Everolimus: 65 Pazopanib: 13 Sunitinib: 7 Other: 1	NR	NR
Hinata[a] 2020[17] (Japan)	Advanced/metastatic RCC N = 208	Nivolumab: 1	Nivolumab: 37	Nivolumab: 31	Nivolumab: 32
Harada[b] 2019[19] (Japan)	Advanced/metastatic RCC N = 266 (1L), 192 (2L), 100 (3L)	TKI: 72 (Sunitinib: 73) mTORi: 14 (Temsirolimus: 92) Cytokines/others: 14 (IFN-α: 84)	TKI-TKI: 52 (Axitinib: 89) TKI-mTORi: 13 (Everolimus: 63) TKI-no treatment: 22	TKI-TKI-TKI: 20 (Pazopanib: 35) TKI-TKI-mTORi: 24 (Everolimus: 75) TKI-TKI-no treatment: 34	NR
Ramaswamy 2017[15,c] (India)	Advanced/metastatic RCC N = 212 (1L), 48 (2L)	Sunitinib: 41 Sorafenib: 38 Pazopanib: 13 Temsirolimus: 3 Everolimus: 2	Everolimus: 13 Pazopanib: 4 Axitinib: 2 Sorafenib: 2 Sunitinib: 1	NR	NR
Lin 2020[20] (Taiwan)	Advanced/metastatic RCC N = 27	Sunitinib: 100	Everolimus: 85 Axitinib: 15	NR	NR

[a]Includes only patients who first received nivolumab and does not capture treatment pattern for other therapies. [b]Only major combinations shown. [c]2L percentages based on N = 212. IFN-α = interferon-alpha.

Table 4. Treatment Pattern Studies in the Adjuvant Setting

Study (Country)	Settings/N	1L, %	2L, %	3L, %	Adjuvant, %
Wang 2017[21] (China)	Adjuvant RCC[a] N = 34	NR	NR	NR	Immunotherapy: 50 No therapy: 27 Targeted therapy: 24
Tiwari 2018[16] (India)	Adjuvant RCC N = 292 (N = 70 on systemic therapy in adjuvant setting)[b]	NR	NR	NR	Systemic therapy: 24 (Sunitinib: 54) (Sorafenib: 21) (Pazopanib: 10) (mTORi: 27) (Immunotherapy: 16)

[a]Xp11.2 translocation/transcription factor E3 gene (TFE3) fusion associated RCC (a rare subtype). [b]These are patients on systemic therapy in an adjuvant setting; however, most patients may not be on any therapy, which is not captured.

RESULTS

Guideline Recommendations

- The few guidelines in APAC that were published between 2016 and 2019 provided varying recommendations on ccRCC management (**Table 5**).[22-24]
- Guidelines from Hong Kong reflected a shift in the 1L systemic treatment of advanced/metastatic ccRCC from standard of care to pembrolizumab plus axitinib over sunitinib for all risk groups.[22] This recommendation was largely based on the outcomes from the immunotherapy-based studies.[5,7]
- There was still uncertainty about the best approach to adjuvant management at the time these guidelines were developed,[22-24] based on a lack of efficacy shown with TKIs, and the need for further clinical evidence on immunotherapies in this setting.[25]

Table 5. Guideline Recommendations for Advanced ccRCC

Guidelines	Population	1L	2L	3L
Poon 2021[22] (Hong Kong)	Advanced/metastatic ccRCC	Pembrolizumab + axitinib (all risk) and nivolumab + ipilimumab (intermediate-poor risk)	2L therapy is determined by 1L therapy	3L therapy based on exclusion of prior agents
2019[23,a] (China)	Advanced/metastatic ccRCC	**High risk:** clinical trial enrollment (Level 1); temsirolimus, cabozantinib, sunitinib (Level 2) **Low-medium risk:** sunitinib, pazopanib, sorafenib (Level 1); axitinib, cabozantinib, bevacizumab + IFN, IFN-α, IL-2 (Level 2)	**1L TKI failure:** axitinib, everolimus (Level 1) **1L cytokine failure:** axitinib, sorafenib, sunitinib, pazopanib (Level 1)	Clinical trial enrollment (Level 1)
Batra 2016[24] (India)	Advanced/metastatic ccRCC	mTORi with everolimus as standard of care	Alternative mTORi or TKI	TKI

[a]Evidence ratings not stated. IL = interleukin.

LIMITATIONS

- This was a systemic review and was limited by time frame, lack of data analysis, and inherent bias in study selection (e.g., language bias). Few studies were identified, particularly in the adjuvant setting, which makes interpretation difficult.
- There were also wide variations in clinical characteristics, and the treatments available may have been impacted by country-specific healthcare systems and cost constraints, which were not taken into consideration.

CONCLUSIONS

- There is an urgent need to monitor treatment outcomes for advanced and adjuvant RCC under real-world settings in APAC; we highlight a clear absence of data.
- There were also few treatment guidelines identified, but they did show a transition towards the use of immunotherapy-based regimens as 1L systemic therapy in advanced ccRCC. This is consistent with US and EU guidelines where they are considered standard of care. However, these recommendations were not evident in clinical practice in APAC.
- Oncologists in APAC are interested in new treatments, including immunotherapy, but there is an urgent need for greater education in this constantly evolving area, including the mechanism of action of new agents in advanced and adjuvant RCC settings.[26]