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Economic Burden of Renal Cell Carcinoma – Part I: An Updated Review

Chun-Ru Chien, MD, PhD^{1,2}, Daniel M. Geynisman, MD³, Bumyang Kim, PhD⁴, Ying Xu, MD, MS⁴, Ya-Chen Tina Shih, PhD⁴

¹Department of Radiation Oncology, China Medical University Hospital, Taichung, Taiwan

²School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

³Department of Medical Oncology, Fox Chase Cancer Center, Temple Health, Philadelphia, PA, USA

⁴Section of Cancer Economics and Policy, Department of Health Services Research, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: The economic burden of renal cell carcinoma (RCC) had been reported to be significant in a previous review published in 2011. The objective of this study is to perform an updated review by synthesizing economic studies related to the treatment of RCC that were published since the previous review.

Methods: We performed a literature search in PubMed, EMBASE, and the Cochrane Library, covering English-language studies published between June 2010 and August 2018. We categorized these articles by type of analyses (cost-effectiveness analysis (CEA), cost analysis, and cost of illness (COI)) and treatment setting (cancer status and treatment), discussed findings from these articles, and synthesized information from each article in summary tables.

Results: We identified 52 studies from 2,317 abstracts/titles deemed relevant from the initial search, including 21 CEA, 23 cost, and 8 COI studies. For localized RCC, costs were found to be positively associated with the aggressiveness of the local treatment. For metastatic RCC (mRCC), pazopanib was reported to be cost-effective in the 1st-line setting. We also found that the economic burden of RCC has increased over time.

Conclusion: RCC continues to impose a substantial economic burden to the healthcare system. Despite the large number of treatment alternatives now available for advanced RCC, the cost-effectiveness and budgetary impact of many new agents remain unknown and warrant greater attention in future research.

Corresponding Author: Ya-Chen Tina Shih, PhD, Professor and Chief, Section of Cancer Economics and Policy, Department of Health Services Research, University of Texas MD Anderson Cancer Center, Mailing Address: 1515 Holcombe Blvd., Unit 1444, Houston, TX 77030, TEL: 713-563-2750; FAX: 713-563-0059; yashih@mdanderson.org.

Data Availability Statement: The data (i.e., Excel file of all abstracts reviewed for this study) generated for the current study are available from the corresponding author upon request.

INTRODUCTION

Kidney cancer is among the top 10 cancers for both men and women in the United States (US), accounting for approximately 4% of new cancer cases estimated in 2018.[1, 2] Globally, the estimated incidence of kidney cancer from GLOBOCAN was 337,860 in 2012.[3] In the US alone, it was estimated that 65,340 new cases of kidney cancer would be diagnosed and 14,970 Americans would die from kidney cancer in 2018.[1, 2] The average age of kidney cancer patients in the US is 64 years old.[4] Overall, men are twice as likely to be diagnosed with kidney cancer as women.[1] Risk factors known to be strongly associated with kidney cancer include obesity and tobacco use; other risk factors are high blood pressure, chronic renal failure, and environmental exposure to chemicals like trichloroethylene.[1] Of the various subtypes of kidney cancer, renal cell carcinoma (RCC) is the predominant form, accounting for 80% - 85% of all kidney cancers.[4] The majority (~65%) of kidney cancers are diagnosed at localized stage, with regional or distant stage each accounting for approximately 16% of the diagnosed cases.[2] The 5-year survival rate for patients with stage I RCC is over 90%; however, the recurrence rate is close to 40% for patients with stage II/III RCC.[4]

For localized RCC, radical nephrectomy (RN) performed as open surgery was the standard of care in the past.[5] As medical technology advances, micro-invasive techniques such as laparoscopic procedures, with or without robotic-assistance, are becoming increasingly common in the surgical treatment of RCC.[5] At the same time, more small or indolent renal cell tumors have been detected as incidental findings while patients underwent imaging for other diseases. For these tumors, concerns have been voiced regarding whether treatment with RN or even partial nephrectomy (PN) may be too invasive and that active surveillance or ablation should be considered as viable alternatives.[5] The role of adjuvant treatment for RCC remains unclear and is currently under active clinical investigation.[6]

For advanced or metastatic RCC (mRCC), systemic treatment is the standard of care, with a subset of patients also benefiting from nephrectomy.[6] Prognostic models have been used to guide treatment selection for patients with RCC.[4, 6] Patients with mRCC have benefited considerably from scientific advances in cancer drug discoveries. As of May 19, 2016, 12 anticancer medications have been approved for the treatment of RCC by the Food and Drug Administration (FDA) in the United States.[7] These drugs include immunotherapy (e.g., high-dose interleukin-2 or checkpoint inhibitors such as nivolumab and ipilimumab), and targeted therapy. Compared to other cancers, a relatively large number of targeted therapy agents, both in oral and infused formulation, are indicated for RCC, including tyrosine kinase inhibitors (TKIs) (e.g., sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, and lenvatinib), anti-vascular endothelial growth factor (anti-VEGF) agents (e.g., bevacizumab) and mammalian target of rapamycin (mTOR) inhibitors (e.g., temsirolimus and everolimus).

A two-part article on the economic burden of RCC was published in *Pharmacoeconomics* in 2011, including a comprehensive review (Part I)[8] and an analysis of databases in the US.[9] This 2011 review article covered studies published between 1 January 2000 and 15 June 2010 and reported substantial economic burden of RCC, with estimated annual costs ranging from \$0.6 billion to \$5.2 billion (2009 US dollars) in the US.[8] Given the technological

advances in oncology in the past 10 years, the high price tag typically associated with new medical technologies, and the influx of new oncologic technologies to the treatment of RCC, the economic burden of RCC is likely to be considerably higher today. The objective of this study is to conduct a comprehensive review of economic studies related to the treatment of RCC for studies published after June 2010 as an update to the review article published in 2011.[8] The economic studies covered in this review include cost, cost-effectiveness, and cost-of-illness studies. This updated review will help patients, clinicians, and payers better understand how the changing landscape of cancer treatment affects the economic burden of RCC.

METHODS

In our updated review, we conducted literature search in PubMed, EMBASE, and the Cochrane Library. Our search covered articles in English language published between June 2010 and August 2018. For searches in PubMed, we combined the search filters recommended in the literature for costs or economic studies.[10] Specifically, we applied the following search terms of costs/economic studies: “((((“costs and cost analysis”[MeSH] OR costs[Title/Abstract] OR cost effective*[Title/Abstract]) OR (cost*[Title/Abstract] OR “costs and cost analysis”[MeSH:noexp] OR cost benefit analys*[Title/Abstract] OR cost-benefit analysis[MeSH] OR health care costs[MeSH:noexp])))).” We then cross-referenced the above search filter with search terms related to RCC “((renal) OR (kidney)) AND ((carcinoma) OR (neoplasm) OR (cancer))” to identify relevant articles. For articles in the Cochrane Library and EMBASE, we modified the search strategy as follows: [((cost.ab or cost.ti or cost.kw) AND ((carcinoma or neoplasm or cancer).ab or (carcinoma or neoplasm or cancer).ti or (carcinoma or neoplasm or cancer).kw) AND ((renal or kidney).ab (renal or kidney).ti or (renal or kidney).kw)) for EMBASE and ((renal) OR (kidney)) AND ((carcinoma) OR (neoplasm) OR (cancer)) AND cost for Cochrane, respectively]. We then removed duplicates identified from different sources, and two independent reviewers (Chien and Shih) reviewed the titles and/or abstracts to select potentially relevant studies. We excluded institution-specific studies because we were interested in the economic burden from the population perspective. In addition, to enhance the clinical relevance of this review regarding the cost-effectiveness of new therapies for RCC, we limited our reviews of cost-effectiveness studies to those that included treatments recommended in current practice guidelines.[6] Disagreement about inclusion of articles in this review was resolved by discussion between the two aforementioned reviewers. Articles to be included in our study were finalized after full-text reviews of the papers identified above. Again, these decisions were made by two independent reviewers (Chien and Shih), with disagreement being resolved through discussion. We applied the 24-item checklist in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement to qualitatively assess articles included in our review.[11]

We categorized the articles identified from the searches above by type of analysis in economic evaluation: cost-effectiveness analysis (CEA), cost analysis, or cost of illness (COI) analysis. We synthesized information retrieved from the literature into the following components in the summary tables: (a) authors, year of publication, country, and sponsorship (i.e., whether the study was sponsored by the manufacturer of the drugs or

devices under investigation); (b) target population (for all studies) and interventions (for CEA or cost studies); (c) study method, including perspective, parameter sources, discounting, cost type, reference year for cost, time frame, and analytical approach; (d) results, including mean costs and mean effectiveness (for CEA studies) for each intervention, and the incremental costs and incremental effectiveness if costs and effectiveness were not reported separately for each intervention; (e) conclusions, including incremental cost-effectiveness ratios (ICERs) and findings from the sensitivity analyses if available; and (f) comments to summarize other elements of the studies that we considered worth noticing.

We used the year reported in the paper as the reference year for cost. If such information was not provided, we then determined the reference year based on the most relevant year of data used, or the year in which the paper was published. All costs in this review were expressed in 2017 US dollars (\$US) in the summary tables, whereas both original and updated dollar values (shown in square brackets if different from the original value) were reported in the text. For studies reporting costs in \$US, we normalized the cost estimates to 2017 values using the medical care services component of the Consumer Price Index.[12] For studies that reported costs in other currencies, we converted the estimates to \$US using the purchasing power parity index (PPP).[13] For the threshold value reported in sensitivity analyses based on currency other than \$US, we quoted the original value as well as \$US converted from the PPP in 2017.

RESULTS

Figure 1 depicts the flowchart of the literature search process as suggested by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14] As shown, we identified 2,317 studies in our initial screening of PubMed, EMBASE, and the Cochrane Library. After removing duplicates (i.e., studies identified from more than one data source), we reviewed the title/abstract to exclude studies that did not meet our inclusion criteria, leaving the remaining 76 articles for full-text review; 52 studies were included in the final analyses. In addition, we also hand-searched the studies included in two systematic reviews [15, 16] identified from our literature search. No additional relevant studies were found from the hand-search. The subsections below are organized by study type: CEA, Cost, and COI (Tables 1–3). Articles within each table are subdivided by cancer stage and treatment characteristics (e.g., line of systemic therapy). Before discussing articles included in our review, we note that only 2 of these 52 articles took a payer's perspective. Table 4 summarizes the qualitative assessment of each article based on the CHEER checklist.

Review of Cost-Effectiveness Analysis (CEA)

Of the 52 studies in our final analysis, 21 studies were cost-effectiveness studies (Table 1). Among the 21 CEA studies that we reviewed, all employed modeling approaches and focused on mRCC patients.

CEA: mRCC 1st-line

Seven articles assessed the first-line treatment of mRCC. Despite a large number of drugs indicated for mRCC, only five drugs were examined in studies comparing the cost-effectiveness of treatment options for current first-line therapy, including pazopanib, sunitinib, sorafenib, interleukin-2, and bevacizumab in combination with interferon-alpha (IFN α). Pazopanib was compared with sunitinib in four studies; [17–20] all obtained clinical information from the COMPARZ (Comparing the Efficacy, Safety and Tolerability of Pazopanib versus Sunitinib) trial, [21] a large phase III non-inferiority international trial sponsored by GlaxoSmithKline — the manufacturer of pazopanib. Delea and colleagues supplemented clinical information retrieved from the COMPARZ trial with the PISCES (Patient Preference Study of Pazopanib versus Sunitinib in Advanced or Metastatic Kidney Cancer) trial which collected information on patient preference, measured by EQ-5D, as the primary endpoint. [17] All four studies employed a partitioned-survival model with three health states (alive with no progression, alive with progression, and dead) and concluded that pazopanib dominated sunitinib.

Another three studies assessing the cost-effectiveness of first-line treatment compared sunitinib with therapeutic alternatives for patients with mRCC prior to sunitinib became available in 2006. [22–24] All three studies concluded that sunitinib was more effective and less costly (i.e., the dominating strategy) when compared to bevacizumab plus IFN α . Two of these three studies also included sorafenib in their assessment; both reported sorafenib was dominated by sunitinib. [22, 23] Interleukin-2 was assessed in Wu et al. (2012) and the authors reported that sunitinib was cost-effective under the Sunitinib Patient Assistance Program. [24]

CEA: mRCC 2nd line

Fourteen cost-effectiveness studies focused on the 2nd-line treatment of mRCC, and assessed the following drugs: sorafenib, everolimus, temsirolimus, sunitinib, nivolumab, cabozantinib, and axitinib. Seven studies also included best supportive care (BSC) as a comparator; [25–31] Of the four studies, all published prior to 2015, that modeled BSC as the “standard of care” none concluded BSC was dominated by the new therapy that it was compared against. [25–28] Two studies that compared sorafenib vs. BSC, both conducted in Cyprus, concluded that the cost-effectiveness of sorafenib largely depended on the drug price. [25, 26] It is worth noticing that of these two studies, one was primarily a value-based pricing study but had also included a CEA component. [26] Mihajlovic and colleagues concluded that everolimus was unlikely to be cost-effective compared to BSC for mRCC patients refractory to sunitinib [27], whereas Paz-Ares and colleagues compared sunitinib with BSC and concluded that sunitinib was cost-effective for mRCC patients who failed first-line therapy with IFN α or interleukin-2. [28]

As more new drugs were approved for second-line therapy of mRCC, BSC became less common in second-line settings and cost-effectiveness analyses were able to model clinical parameters from head-to-head trials, such as the AXIS (AXitinib vs. Sorafenib in advanced renal cell carcinoma) trial for axitinib vs. sorafenib [32] and the CheckMate 025 trial for nivolumab vs. everolimus. [33] Eight studies included both nivolumab and everolimus in the

comparators [29–31, 34–38] and these two drugs were directly compared in six.[29, 31, 34–36, 38]. Only two out of the six studies found nivolumab to be cost effective compared to everolimus. Specifically, Giuliani and colleagues reported an ICER around \$2,400 per month of life gained for nivolumab compared to everolimus [29] and McCrea and colleagues estimated the ICER to be close to \$52,000 per quality-adjusted life year (QALY) gained.[35] The other four studies concluded that nivolumab was unlikely to be more cost effective than everolimus when benchmarking against the societal willingness to pay (WTP) of \$100,000/QALY.[31, 34, 36, 38] It is worth noting that the study by Giuliani et al. may reflect a partial assessment because their analyses only considered drug cost.[29] Comparisons between cabozantinib and everolimus were identified in three studies; all three reported ICER higher than \$150,000 per QALY or LY when cabozantinib was compared to everolimus.[30, 37, 38] Collectively, the literature to date is leaning toward less favorable cost-effectiveness conclusions for newly approved agents for second-line treatment of mRCC, such as cabozantinib and nivolumab, when compared to everolimus.

Two cost-effectiveness analyses modeled sorafenib as the standard of care for second-line therapy. When compared to sorafenib, Casciano and colleagues concluded that everolimus was cost-effective for mRCC patients refractory to sunitinib,[39] whereas Petrou reported that it would take a WTP threshold higher than €100,000 for axinitib to be cost-effective. [40] In addition to the above study by Petrou[40], the cost-effectiveness of axinitib vs. other second-line agents was examined in four other studies.[29, 30, 37, 38] Axinitib was found to be dominated by everolimus in Edwards et al. (2018)[30] and Swallow et al. (2018)[38] and by sorafenib in Giuliani et al. (2018).[29] When cabozantinib was compared to axinitib, Meng and colleagues reported an ICER of \$142,194 [98,967 GBP/QALY] per QALY gained, indicating that cabozantinib was not more cost effective compared to axinitib.[37]

Review of Cost Analysis

Our literature search identified 23 cost studies (Table 2). The majority of these studies were observational studies using secondary databases available in the US. The most commonly used database in US-based studies is Surveillance, Epidemiology, and End Results (SEER)-Medicare data, which link cancer patients in the SEER Program, an epidemiological surveillance system of population-based tumor registries containing data from 17 geographic areas in the US, with a Medicare enrollment file to identify cancer patients in the SEER registry who were eligible for Medicare, and to collect all Medicare claims for these patients in the database.[41] For studies using claims data, insurance payment was used to quantify costs.

Cost: localized RCC

Eight studies focused on treatment for localized stage RCC.[42–49] As discussed earlier, surgery remains the mainstay of treatment for early stage RCC; therefore, all eight studies (1 UK, 6 US, 1 Taiwan) included some form of surgical procedure. Four articles compared open radical nephrectomy (ORN) with laparoscopic radical nephrectomy (LRN) or minimally invasive radical nephrectomy (MIRN).[44–46, 49] Using data from the Nationwide Inpatient Sample,[45] the SEER-Medicare,[44, 46] and the National Health Insurance Research Database of Taiwan,[49] three of the four studies concluded that costs

were comparable between ORN and LRN or MIRN.[44, 45, 49] Among LRN, Golombos and colleagues reported that robotic-assisted RN was associated with higher cost when compared to LRN without robotic assistance.[43] An opposite conclusion was reached in a UK study on partial nephrectomy (PN); Camp and colleagues reported that costs of robotic-assisted PN was lower than open PN or LPN without robotic assistance.[42] A similar comparison was made in Bahler et al. (2018) based on a US database[48]; the authors found that RPN had significantly higher costs than OPN although the cost difference became statistically insignificant toward the end of their study period. It is worth noting that of the eight cost studies that compared various forms of surgical techniques, Camp et al. (2018) was the only study sponsored by Intuitive Surgical Inc., the sole manufacture of robotic surgical systems.[42]

Kowalczyk et al. (2013) and Larcher et al. (2017) compared nephrectomy with less aggressive management of localized RCC with small tumor size, such as ablation or surveillance.[46, 47] Both studies analyzed SEER-Medicare data and reported higher costs of nephrectomy. The study that included surveillance as a viable option for patients with small renal masses concluded that surveillance was associated with lowest cost, followed by ablation then nephrectomy.[46]

Cost: non-pharmaceutical treatment of mRCC

Among the fifteen cost studies of mRCC, only one focused on surgical management of mRCC [50]; all others examined anticancer medications. Takagi and colleagues conducted a population-based study using a Japanese database to explore factors associated with perioperative outcomes of cytoreductive nephrectomy for mRCC and concluded that total hospitalization cost of laparoscopic nephrectomy was 3.4% higher than that of open nephrectomy.[50]

Cost: mRCC, pharmaceutical treatments, 1st-line

Of the eight studies that estimated the costs of anticancer medications as the first-line therapy, six compared pazopanib to sunitinib. Despite the difference in study approaches and the definition of costs, all six studies concluded that pazopanib had lower cost, [51–56] with the magnitude of annual cost difference ranging from less than \$7,200 per patient [52] to over \$20,000 (in 2017 US\$).[54] Ravasio and colleagues compared sunitinib vs. bevacizumab plus IFN α from the perspective of the Italian National Health Service (NHS) and found sunitinib to be associated with higher cost.[57] The authors noted that the cost advantage of IFN α could be driven by the terms of the risk-sharing agreement between the Italian NHS and the manufacturer of bevacizumab vs. that of sunitinib.[57] Instead of comparing specific agents for mRCC, Soerensen and colleagues compared two classes of anticancer medications in first-line settings from both payers' and societal perspectives: traditional cytokine immunotherapy (e.g., interleukin-2) vs. targeted therapies.[58] This Danish study found that although drug costs were substantially higher for mRCC patients receiving targeted therapies than those receiving immunotherapy, total healthcare costs were not significantly different between these two groups as higher drug costs of targeted therapies were offset by lower inpatient and radiotherapy costs.[58]

Cost: mRCC, pharmaceutical treatments, 2nd-line

Two cost studies focused on 2nd-line treatment for mRCC.[59, 60] Both were US studies and compared axitinib to everolimus. Perrin and colleagues applied a modeling approach to project lifetime costs,[60] whereas Pal and colleagues conducted a retrospective review of medical records to estimate costs per month of progression-free survival.[59] both concluded that axitinib had higher costs than everolimus.[59, 60] However, one must exercise caution when interpreting these findings because certain input parameters in Perrin et al. appeared to be biased against axitinib (e.g., longer duration of drug supply for axitinib) and the study by Pal et al. only reflected drug acquisition costs.

Cost: mRCC, pharmaceutical treatments, all lines

Four cost studies explored treatment costs of mRCC associated with different dosing patterns or treatment pathways without focusing on specific lines of therapy. Sou and colleagues explored clinical outcomes and costs associated with various modifications of dose and/or schedule of sunitinib to make the drug better tolerated by mRCC patients.[61] Compared to the standard schedule of 50 mg daily, 4 weeks on/2 weeks off, the study found that several adjusted-dose sunitinib regimens were associated with lower costs and improved overall as well as progression free survival.[61] Geynisman and colleagues stratified patients by whether their first-line treatment of mRCC was an oral or intravenous (IV) agent and compared the treatment patterns and costs within the first year since treatment initiation.[62] The authors further subdivided patients in the IV group by whether their treatment regimen consisted of one or more targeted IV anticancer medications (i.e., bevacizumab or temsirolimus).[62] The authors reported a six-fold increase in median drug costs from 2004 to 2010, with the average cost per patient exceeding \$140,000 (in 2017 \$US) in the first year of treatment. Shi and colleagues compared costs associated with different treatment sequences started with sunitinib and reported that 1st-line sunitinib followed by axitinib as 2nd-line therapy was the lowest cost sequence for Chinese patients with mRCC.[63] Maroun and colleagues surveyed oncologists in France on the treatment patterns, durations, and costs for mRCC patients who had targeted therapy as first-line treatment and reported a wide range of daily costs of targeted therapy across agents and line of therapy.[64]

Review of Cost of Illness Studies

We identified eight studies that estimated the economic burden of RCC (Table 3). Of those, only one study included all tumor stages,[65] and the remaining seven focused only on patients with mRCC and two further limited their analyses to costs of adverse events associated with targeted therapies used to treat mRCC.

COI: all stages

Hollenbeak and colleagues analyzed SEER-Medicare data, 1995–2002, and used statistical methods that accounted for censored cost data [66, 67] to estimate the cumulative costs for newly diagnosed elderly RCC patients at 1 and 5 years.[65] The authors applied a net costing approach [68, 69] by identifying a non-cancer control cohort using propensity score matching method and estimated RCC-related costs as the difference between the mean cost of the RCC cohort and that of the matched non-cancer controls. The cumulative costs for the

RCC group were \$33,685 (2005 US\$) [\$49,540, in 2017 US\$] at 1 year and \$110,798 [\$162,948] at 5 years. The cost difference between the RCC and the matched control at year 1 was \$24,424 [\$35,920] in unadjusted analysis and \$22,340 [\$32,855] in adjusted analysis (adjusting for censoring and controlling for covariates), and was \$48,026 [\$70,631] and \$20,976 [\$30,849], respectively, at year 5.

COI: mRCC

The approval of several targeted therapy agents for mRCC has motivated researchers to study the economic impact of these costly agents on this particular disease stage of RCC. Although this topic was explored in five studies,[70–74] comparing economic burden estimated from these studies was not meaningful because of differences in the study cohorts and variations in cost structure across countries, as well as what was captured in costs. Ballali and colleagues estimated the population economic burden for mRCC patients in Italy but restricted their study to the clinical scenario of using sunitinib and sorafenib as first- and second-line treatment, respectively. The estimated population drug costs for the above scenario was over 5 million dollars for the first year of treatment.[70] Maroun and colleagues explored the impact of targeted therapy on inpatient costs of mRCC in France by comparing costs of hospital management between patient cohorts in two time periods (2008 vs. 2012). The study concluded that although the mean hospitalization cost per patient continued to increase over time, the proportion of patients receiving expensive IV drugs in hospital setting has decreased as a result of increasing use of targeted oral anticancer drugs. [72] Another French study estimated per patient per month (PPPM) costs for mRCC patients receiving targeted therapies as first-line treatment and reported that costs of targeted oral agents accounted for more than 50% of the estimated total PPPM cost of €5,546 [\$6,944]. [71] From the societal perspective, Purmonen and colleagues estimated the lifetime treatment costs of mRCC patients who received IFN α as first-line treatment and conducted budget impact modeling to project the impact of adding sunitinib to the 1st-line treatment protocol on the five year costs of mRCC in Finland. The estimated lifetime costs with IFN α was €32,951 [\$41,253] and the addition of sunitinib was projected to raise the 5-year national budget from €26 million [\$33 million] to €41M (\$51 million).[73] Li and colleagues focused on the out-of-pocket (OOP) cost for Medicare beneficiaries enrolled in the Medicare prescription drug plans (also known as Part D) and reported OOP costs to be substantially lower for those with low-income subsidies compared to those without subsidies (\$8 vs. \$3,208 per month).[74]

COI: adverse events associated with targeted therapies for mRCC

The economic burden of adverse events (AE) associated with targeted therapies was examined in two studies.[75, 76] Both studies were observational studies that focused on grade 3 or 4 toxicities with 5% occurrence as reported in the trials of any of the four targeted therapy agents (sunitinib, sorafenib, bevacizumab, and pazopanib); data were limited to AE that could be ascertained from claims data. AE captured in both studies included abdominal pain, back pain, diarrhea, dyspnea, extremity pain, fatigue/asthenia, hand-foot syndrome, hypertension, lymphopenia, nausea/vomiting, neutropenia, proteinuria, and thrombocytopenia. Instead of directly quantifying costs associated with each AE, both studies estimated the economic burden of targeted therapy-related AEs using the difference

in the total healthcare costs (not including costs of targeted therapies) within 30 days of the occurrence of AE between patients with AE and those without, with ‘shadow’ index dates assigned to the latter group. After adjusting for differences in patient characteristics between the AE and non-AE groups, the estimated costs of AE ranged between \$11,373 [\$12,716] among non-elderly, privately insured mRCC patients [75] and \$12,410 [\$13,875] among elderly mRCC patients enrolled in Medicare.[76]

Assessment based on CHEERS Checklist

The qualitative assessment of each article based on the 24-item CHEERS checklist is provided in the supplementary tables and summarized in Table 4. Overall, the quality of these studies was acceptable per criteria set forth in the CHEERS checklist. With the exception of the study by Guiliani et al. (2018)[29], the number of checklist items not addressed in the articles was four or less. In terms of compliance with specific checklist items, most items were addressed by the vast majority of articles included in our review, except for two items: characterizing heterogeneity and currency, price date, and conversion. Specifically, 41 of the 52 articles (~79%) did not examine heterogeneity by exploring the extent to which the differences in costs or cost-effectiveness could be explained by variations in patients’ baseline characteristics or other factors, whereas approximately 21% (11 of 52) of the studies did not provide sufficient information on the referenced date of costs or methods to normalize costs to a particular year, or the exchange rates used in currency conversion.

DISCUSSION

The literature search performed for this updated review indicates a growing research interest in the cancer economics of RCC, as demonstrated by more than double the number of studies (n=52) identified from our current search of articles published between June 2010 and August 2018, compared to 20 studies in our previous review that covered the duration between January 2000 and June 2010. Table 5 summarizes the characteristics of the 52 articles included in this updated review. All but five studies [24, 34, 49, 50, 63] were from authors in Europe or North America, especially in the US (n=25). Almost half of the studies (n=25) were sponsored by the manufacturer of the drug or surgical device under investigation and more than 80% (n=43) of the studies focused on mRCC. Although the societal perspective is recommended for economic evaluation of healthcare and cost-effectiveness analyses,[77] the vast majority of the studies took the perspective of the healthcare sector. Overall, modeling was the dominant analytical approach in CEA whereas most cost and COI studies were observational studies using secondary databases.

Our review of CEA studies found that as 1st-line treatment for mRCC pazopanib dominated sunitinib, which further dominated bevacizumab plus IFN α as well as sorafenib. Findings from CEA of 2nd-line treatment were less conclusive as the cost-effectiveness of a specific agent varied by drug cost or WTP threshold. All CEA identified from our literature search focused on comparing pharmacological treatments. Perhaps because there was no evidence demonstrating the efficacy of any particular anticancer medication in the adjuvant setting for

RCC except for the recent approval of adjuvant sunitinib by the FDA in the US,[78] all CEA focused on patients with advanced or metastatic RCC.

Several observations in our review of CEA studies warrant further discussion. First, the treatment of RCC, especially mRCC, has dramatically changed in the past decades to the extent that CEA quickly became outdated. For example, our previous review had concluded that sunitinib was likely to be cost-effective in both 1st- and 2nd-line settings.[7] However, the current review found several studies that concluded that compared to sunitinib, pazotinib, a new drug that was not available in our previous review in 2011, was more cost-effective in the 1st-line setting. Also, many recently published studies that assessed the cost-effectiveness of 2nd-line therapies no longer included sunitinib as a comparator. For diseases with a large influx of new treatments, it is important to reassess and update the cost-effectiveness literature to stay clinically relevant. Second, although there are close to 20 guideline compatible treatment alternatives for mRCC, only 10 agents have been examined in CEA. This suggests a large knowledge gap on the cost-effectiveness of the wide array of treatment options for patients with mRCC. Third, some treatments that may not appear to be cost-effective in all settings such as nivolumab, present a tremendous clinical benefit for a minority of patients (the ‘tail of the curve’) and cannot be properly captured in traditional CEA. Lastly, even among the small subset of agents that were better covered in the CEA literature, a high level of repetition was observed. For example, four studies in our review employed nearly identical modeling approaches and had a large proportion of overlapping authors across studies. Of the four studies, the first was published in 2015 using a US-based model.[17] It is reasonable to consider the three studies published subsequent to the first study as country adaptation studies that extended the original model to Canada,[18] United Kingdom,[19] and Italy.[20] These rather homogeneous CEA studies raised concern on the representativeness and generalizability of their findings, especially when all studies had the same commercial sponsor with several coauthors from the same research group. Researchers must exercise caution not to draw cost-effectiveness conclusions by simply comparing the number of studies with favorable vs. unfavorable economic findings without carefully assessing the representativeness and generalizability of evidence from country adaptation studies produced by the same research team.

Collectively, findings from cost studies of localized stage RCC agreed that costs tended to rise with the aggressiveness of the local treatment. For radical nephrectomy, minimally invasive surgical techniques, such as laparoscopic with or without robotic-assistance, were not necessarily associated with cost saving. However, for partial nephrectomy, robotic-assisted laparoscopic techniques appeared to have a cost advantage. This finding is consistent with what was reported in our previous review, in which laparoscopic PN was found to be cost-saving compared to open PN.[8] The cost advantage of robotic-assisted procedures observed in PN might be partly due to the advanced technology filling the void of a greater need for improvement in the surgical skill required for PN (as compared to RN). [79]

Three caveats for using the findings from our review to assist reimbursement decisions or guide clinical practice and future research are discussed below. First, the external validity to regions outside North America and Europe must be considered as only 10% (5 out of 52) of

the studies were from these regions. Second, although recent guidelines have different treatment recommendations for clear cell and non-clear cell mRCC,[5] our review did not differentiate these two subtypes of mRCC because this level of clinical detail was not provided in the studies we reviewed. Lastly, our quality assessment indicated that while the studies had largely met the reporting standards of the CHEERS checklist, one item that needs attention in future research is to better characterize heterogeneity as it was addressed by around 20% of the studies in this review. The importance of subgroup analyses to understand heterogeneity is becoming increasingly important in economic studies in the era of personalized medicine.

CONCLUSION

In summary, RCC continued to exert considerable economic burden to the healthcare system. Although the treatment alternatives for RCC, especially mRCC, have substantially expanded in the past two decades, the cost-effectiveness and budgetary impact of many new agents remain unexplored and represent areas in urgent need for future research to help patients, clinicians, and payers better navigate the changing landscape of treatment for RCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. ACS. Cancer Facts & Figures 2018. Atlanta, GA: American Cancer Society; 2018.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018 1;68(1):7–30. [PubMed: 29313949]
3. IARC. Estimated number of incident cases, both sexes, kidney cancer, worldwide in 2012. [cited 2018 April 17]; Available from: https://gco.iarc.fr/today/online-analysis-table?mode=population&mode_population=continents&population=900&sex=0&cancer=21&type=0&statistic=0&prevalence=0&color_palette=default,%20accessed%202018%2F3%2F3
4. Barata PC, Rini BI. Treatment of renal cell carcinoma: Current status and future directions. *CA Cancer J Clin* 2017 11;67(6):507–24. [PubMed: 28961310]
5. Curti BD. Renal cell carcinoma. *JAMA* 2004 7 7;292(1):97–100. [PubMed: 15238597]
6. NCCN. NCCN Guidelines with NCCN Evidence Blocks: Clinical Practice Guidelines in Oncology: Kidney Cancer Version 4.2018. 2018 [cited 2018 May 1]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf

7. NCI. Drugs Approved for Kidney (Renal Cell) Cancer. 2018 [cited 2018 April 10]; Available from: <https://www.cancer.gov/about-cancer/treatment/drugs/kidney>
8. Shih YC, Chien CR, Xu Y, Pan IW, Smith GL, Buchholz TA. Economic burden of renal cell carcinoma: Part I--an updated review. *Pharmacoeconomics*. 2011 4;29(4):315–29. [PubMed: 21395351]
9. Shih YC, Chien CR, Xu Y, Pan IW, Smith GL, Buchholz TA. Economic burden of renal cell carcinoma in the US: Part II--an updated analysis. *Pharmacoeconomics*. 2011 4;29(4):331–41. [PubMed: 21395352]
10. HIRU. Search Filters for MEDLINE in Ovid Syntax and the PubMed translation.
11. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013 325;346:f1049. [PubMed: 23529982]
12. BLS. CPI Databases. [cited 2018 March 10]; Available from: <https://www.bls.gov/cpi/data.htm>
13. IMF. World Economic Outlook database. 2017 [cited 2018 April 30]; Available from: <http://www.imf.org/external/pubs/ft/weo/2017/02/weodata/download.aspx>
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015 11;4:1. [PubMed: 25554246]
15. Purmonen TT. Cost-effectiveness of sunitinib in metastatic renal cell carcinoma. *Expert Rev Pharmacoecon Outcomes Res* 2011 8;11(4):383–93. [PubMed: 21831017]
16. Petrou P A systematic review of economic evaluations of tyrosine kinase inhibitors of vascular endothelial growth factor receptors, mammalian target of rapamycin inhibitors and programmed death-1 inhibitors in metastatic renal cell cancer. *Expert Rev Pharmacoecon Outcomes Res* 2018 6;18(3):255–65. [PubMed: 29448845]
17. Delea TE, Amdahl J, Diaz J, Nakhaipour HR, Hackshaw MD. Cost-effectiveness of pazopanib versus sunitinib for renal cancer in the United States. *J Manag Care Spec Pharm* 2015 1;21(1):46–54, a-b. [PubMed: 25562772]
18. Amdahl J, Diaz J, Park J, Nakhaipour HR, Delea TE. Cost-effectiveness of pazopanib compared with sunitinib in metastatic renal cell carcinoma in Canada. *Curr Oncol* 2016 8;23(4):e340–54. [PubMed: 27536183]
19. Amdahl J, Diaz J, Sharma A, Park J, Chandiwana D, Delea TE. Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in the United Kingdom. *PLoS One*. 2017;12(6):e0175920. [PubMed: 28636648]
20. Capri S, Porta C, Delea TE. Cost-effectiveness of Pazopanib Versus Sunitinib as First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma from an Italian National Health Service Perspective. *Clin Ther* 2017 3;39(3):567–80 e2. [PubMed: 28189363]
21. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013 8 22;369(8):722–31. [PubMed: 23964934]
22. Calvo Aller E, Maroto P, Kreif N, Gonzalez Larriba JL, Lopez-Brea M, Castellano D, et al. Cost-effectiveness evaluation of sunitinib as first-line targeted therapy for metastatic renal cell carcinoma in Spain. *Clin Transl Oncol*. 2011 12;13(12):869–77. [PubMed: 22126730]
23. Benedict A, Figlin RA, Sandstrom P, Harmenberg U, Ullen A, Charbonneau C, et al. Economic evaluation of new targeted therapies for the first-line treatment of patients with metastatic renal cell carcinoma. *BJU Int* 2011 9;108(5):665–72. [PubMed: 21265994]
24. Wu B, Dong B, Xu Y, Zhang Q, Shen J, Chen H, et al. Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. *PLoS One*. 2012;7(3):e32530. [PubMed: 22412884]
25. Petrou PK, Talias MA. Cost-effectiveness of sorafenib compared to best supportive care in second line renal cell cancer from a payer perspective in Cyprus. *Expert Rev Pharmacoecon Outcomes Res* 2014 2;14(1):131–8. [PubMed: 24397606]
26. Petrou P, Talias MA. A pilot study to assess feasibility of value based pricing in Cyprus through pharmacoeconomic modelling and assessment of its operational framework: sorafenib for second line renal cell cancer. *Cost Eff Resour Alloc* 2014;12:12. [PubMed: 24910539]

27. Mihajlovic J, Pechlivanoglou P, Sabo A, Tomic Z, Postma MJ. Cost-effectiveness of everolimus for second-line treatment of metastatic renal cell carcinoma in Serbia. *Clin Ther* 2013 12;35(12): 1909–22. [PubMed: 24238790]
28. Paz-Ares L, del Muro JG, Grande E, Diaz S. A cost-effectiveness analysis of sunitinib in patients with metastatic renal cell carcinoma intolerant to or experiencing disease progression on immunotherapy: perspective of the Spanish National Health System. *J Clin Pharm Ther* 2010 8;35(4):429–38. [PubMed: 20831545]
29. Giuliani J, Bonetti A. Nivolumab Is a Cost-Effective Second-Line Treatment for Metastatic Renal-Cell Carcinoma. *Clin Genitourin Cancer*. 2018 6;16(3):e557–e62. [PubMed: 29534940]
30. Edwards SJ, Wakefield V, Cain P, Karner C, Kew K, Bacelar M, et al. Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation. *Health Technol Assess* 2018 1;22(6):1–278.
31. Sarfaty M, Leshno M, Gordon N, Moore A, Neiman V, Rosenbaum E, et al. Cost Effectiveness of Nivolumab in Advanced Renal Cell Carcinoma. *Eur Urol* 2018 4;73(4):628–34. [PubMed: 28807351]
32. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013 5;14(6):552–62. [PubMed: 23598172]
33. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015 11 5;373(19):1803–13. [PubMed: 26406148]
34. Wan XM, Peng LB, Ma JA, Li YJ. Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and Chinese perspectives. *Cancer*. 2017 7 15;123(14): 2634–41. [PubMed: 28301684]
35. McCrea C, Johal S, Yang S, Doan J. Cost-effectiveness of nivolumab in patients with advanced renal cell carcinoma treated in the United States. *Exp Hematol Oncol* 2018;7:4. [PubMed: 29456880]
36. Raphael J, Sun Z, Bjarnason GA, Helou J, Sander B, Naimark DM. Nivolumab in the Treatment of Metastatic Renal Cell Carcinoma: A Cost-Utility Analysis. *Am J Clin Oncol* 2018 5 4.
37. Meng J, Lister J, Vataire AL, Casciano R, Dinot J. Cost-effectiveness comparison of cabozantinib with everolimus, axitinib, and nivolumab in the treatment of advanced renal cell carcinoma following the failure of prior therapy in England. *Clinicoecon Outcomes Res* 2018;10:243–50. [PubMed: 29719414]
38. Swallow E, Messali A, Ghate S, McDonald E, Duchesneau E, Perez JR. The Additional Costs per Month of Progression-Free Survival and Overall Survival: An Economic Model Comparing Everolimus with Cabozantinib, Nivolumab, and Axitinib for Second-Line Treatment of Metastatic Renal Cell Carcinoma. *J Manag Care Spec Pharm* 2018 4;24(4):335–43. [PubMed: 29578848]
39. Casciano R, Chulikavit M, Di Lorenzo G, Liu Z, Baladi JF, Wang X, et al. Economic evaluation of everolimus versus sorafenib for the treatment of metastatic renal cell carcinoma after failure of first-line sunitinib. *Value Health*. 2011 Sep-Oct;14(6):846–51. [PubMed: 21914504]
40. Petrou P Cost-effectiveness analysis of axitinib through a probabilistic decision model. *Expert Opin Pharmacother*. 2015 6;16(8):1233–43. [PubMed: 25958963]
41. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002 8;40(8 Suppl):IV-3–18.
42. Camp C, O'Hara J, Hughes D, Adshead J. Short-term Outcomes and Costs Following Partial Nephrectomy in England: A Population-based Study. *Eur Urol Focus*. 2017 4 8.
43. Golombos DM, Chughtai B, Trinh QD, Mao J, Te A, O'Malley P, et al. Adoption of Technology and Its Impact on Nephrectomy Outcomes, a U.S. Population-Based Analysis (2008–2012). *J Endourol* 2017 1;31(1):91–9. [PubMed: 27809567]

44. Golombos DM, Chughtai B, Trinh QD, Thomas D, Mao J, Te A, et al. Minimally invasive vs open nephrectomy in the modern era: does approach matter? *World J Urol* 2017 10;35(10):1557–68. [PubMed: 28477204]
45. Kim SP, Leibovich BC, Shah ND, Weight CJ, Borah BJ, Han LC, et al. The relationship of postoperative complications with in-hospital outcomes and costs after renal surgery for kidney cancer. *BJU Int* 2013 4;111(4):580–8. [PubMed: 22564425]
46. Kowalczyk KJ, Choueiri TK, Hevelone ND, Trinh QD, Lipsitz SR, Nguyen PL, et al. Comparative effectiveness, costs and trends in treatment of small renal masses from 2005 to 2007. *BJU Int* 2013 8;112(4):E273–80. [PubMed: 23452093]
47. Larcher A, Sun M, Dell'Oglio P, Trudeau V, Boehm K, Schiffmann J, et al. Mortality, morbidity and healthcare expenditures after local tumour ablation or partial nephrectomy for T1A kidney cancer. *Eur J Surg Oncol* 2017 4;43(4):815–22. [PubMed: 27692535]
48. Bahler CD, Monn MF, Flack CK, Gramm AR, Gardner TA, Sundaram CP. Assessing Cost of Robotic Utilization in Partial Nephrectomy with Increasing Utilization. *J Endourol* 2018 8;32(8):710–6. [PubMed: 29943664]
49. Chang YH, Chang SW, Liu CY, Lin PH, Yu KJ, Pang ST, et al. Demographic characteristics and complications of open and minimally invasive surgeries for renal cell carcinoma: a population-based case-control study in Taiwan. *Ther Clin Risk Manag* 2018;14:1235–41. [PubMed: 30038497]
50. Takagi T, Sugihara T, Yasunaga H, Horiguchi H, Fushimi K, Kondo T, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma: a population-based analysis of perioperative outcomes according to clinical stage. *Int J Urol* 2014 8;21(8):770–5. [PubMed: 24712555]
51. Villa G, Hernandez-Pastor LJ. Budget impact analysis of first-line treatment with pazopanib for advanced renal cell carcinoma in Spain. *BMC Cancer*. 2013 9 2;13:399. [PubMed: 24004638]
52. Hansen RN, Hackshaw MD, Nagar SP, Arondekar B, Deen KC, Sullivan SD, et al. Health care costs among renal cancer patients using pazopanib and sunitinib. *J Manag Care Spec Pharm* 2015 1;21(1):37–44, a-d. [PubMed: 25562771]
53. MacLean E, Mardekian J, Cisar LA, Hoang CJ, Harnett J. Real-World Treatment Patterns and Costs for Patients with Renal Cell Carcinoma Initiating Treatment with Sunitinib and Pazopanib. *J Manag Care Spec Pharm* 2016 8;22(8):979–90. [PubMed: 27459661]
54. Vogelzang NJ, Pal SK, Ghate SR, Swallow E, Li N, Peeples M, et al. Clinical and Economic Outcomes in Elderly Advanced Renal Cell Carcinoma Patients Starting Pazopanib or Sunitinib Treatment: A Retrospective Medicare Claims Analysis. *Adv Ther* 2017 11;34(11):2452–65. [PubMed: 29076108]
55. Racsa PN, Whisman TR, Worley K. Comparing two tyrosine kinase inhibitors for treatment of advanced renal cell carcinoma in Medicare and commercially insured patients. *Curr Med Res Opin* 2015;31(10):1933–40. [PubMed: 26368665]
56. Vogelzang NJ, Pal SK, Ghate SR, Li N, Swallow E, Peeples M, et al. Real-World Economic Outcomes During Time on Treatment Among Patients Who Initiated Sunitinib or Pazopanib as First Targeted Therapy for Advanced Renal Cell Carcinoma: A Retrospective Analysis of Medicare Claims Data. *J Manag Care Spec Pharm* 2018 6;24(6):525–33. [PubMed: 29799328]
57. Ravasio R, Ortega C, Sabbatini R, Porta C. Bevacizumab plus interferon-alpha versus sunitinib for first-line treatment of renal cell carcinoma in Italy: a cost-minimization analysis. *Clin Drug Investig* 2011;31(7):507–17.
58. Soerensen AV, Donskov F, Kjellberg J, Ibsen R, Hermann GG, Jensen NV, et al. Health economic changes as a result of implementation of targeted therapy for metastatic renal cell carcinoma: national results from DARENCA study 2. *Eur Urol* 2015 9;68(3):516–22. [PubMed: 25533417]
59. Pal SK, Jonasch E, Signorovitch JE, Reichmann WM, Li N, Liu Z, et al. Real-world dosing and drug costs with everolimus or axitinib as second targeted therapies for advanced renal cell carcinoma: a retrospective chart review in the US. *J Med Econ* 2016;19(5):462–8. [PubMed: 26652893]
60. Perrin A, Sherman S, Pal S, Chua A, Gorritz M, Liu Z, et al. Lifetime cost of everolimus vs axitinib in patients with advanced renal cell carcinoma who failed prior sunitinib therapy in the US. *J Med Econ* 2015 3;18(3):200–9. [PubMed: 25422989]

61. Suo A, Iqbal U, Lim J, Lee C, Gesy K, Iqbal N, et al. Outcomes and Drug Costs of Sunitinib Regimens for Metastatic Renal Cell Carcinoma: A Provincial Population-Based Study. *Clin Genitourin Cancer*. 2017 6;15(3):e397–e404. [PubMed: 28216279]
62. Geynisman DM, Hu JC, Liu L, Tina Shih YC. Treatment patterns and costs for metastatic renal cell carcinoma patients with private insurance in the United States. *Clin Genitourin Cancer*. 2015 4;13(2):e93–100. [PubMed: 25450038]
63. Shi G, Park SH, Ren H, Xue M, Lu X, Dong P, et al. Cost analysis for different sequential treatment regimens for metastatic renal cell carcinoma in China. *J Med Econ* 2018 9 10:1–9.
64. Maroun R, Mitrofan L, Benjamin L, Nachbaur G, Maunoury F, Le Jeunne P, et al. Real life patterns of care and progression free survival in metastatic renal cell carcinoma patients: retrospective analysis of cross-sectional data. *BMC Cancer*. 2018 2 21;18(1):214. [PubMed: 29466966]
65. Hollenbeak CS, Nikkel LE, Schaefer EW, Alemao E, Ghahramani N, Raman JD. Determinants of medicare all-cause costs among elderly patients with renal cell carcinoma. *J Manag Care Pharm* 2011 10;17(8):610–20. [PubMed: 21942302]
66. Lin DY. Linear regression analysis of censored medical costs. *Biostatistics*. 2000 3;1(1):35–47. [PubMed: 12933524]
67. Bang H, Tsiatis AA. Estimating medical costs with censored data. *Biometrika*. 2000;87(2):329–43.
68. Brown ML, Riley GF, Schussler N, Etzioni R. Estimating health care costs related to cancer treatment from SEER-Medicare data. *Med Care*. 2002 8;40(8 Suppl):IV-104–17.
69. Barlow WE. Overview of methods to estimate the medical costs of cancer. *Med Care*. 2009 7;47(7 Suppl 1):S33–6. [PubMed: 19536013]
70. Ballali S, Chiffi D, Trojniak MP, Gregori D, Agreement tE-VRP. Economic Impact of Sunitinib and Sorafenib Use in Metastatic Renal Cell Carcinoma Treatment in Veneto Region, Italy. *Open Pharmacology Journal*. 2013;7(Suppl 1: M2):2–8.
71. Maroun R, Fleury L, Nachbaur G, Maunoury F, Vanhille JL, Durand-Zaleski I. Real-world costs and outcomes in metastatic renal cell carcinoma patients treated with targeted therapies: a cohort study from the French health insurance database. *Curr Med Res Opin* 2017 10;33(10):1755–62. [PubMed: 28748721]
72. Maroun R, Maunoury F, Benjamin L, Nachbaur G, Durand-Zaleski I. In-Hospital Economic Burden of Metastatic Renal Cell Carcinoma in France in the Era of Targeted Therapies: Analysis of the French National Hospital Database from 2008 to 2013. *PLoS One*. 2016;11(9):e0162864. [PubMed: 27649305]
73. Purmonen T, Nuttunen P, Vuorinen R, Pyrhonen S, Kataja V, Kellokumpu-Lehtinen P. Current and predicted cost of metastatic renal cell carcinoma in Finland. *Acta Oncol* 2010 8;49(6):837–43. [PubMed: 20331406]
74. Li P, Wong YN, Jahnke J, Pettit AR, Doshi JA. Association of high cost sharing and targeted therapy initiation among elderly Medicare patients with metastatic renal cell carcinoma. *Cancer Med* 2018 1;7(1):75–86. [PubMed: 29195016]
75. Hagiwara M, Borker R, Oster G. Economic burden of adverse events in patients with metastatic renal cell carcinoma. *Clin Ther* 2013 12;35(12):1955–63 e2. [PubMed: 24290735]
76. Hagiwara M, Hackshaw MD, Oster G. Economic burden of selected adverse events in patients aged ≥ 65 years with metastatic renal cell carcinoma. *J Med Econ* 2013 11;16(11):1300–6. [PubMed: 24004437]
77. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York, NY: Oxford University Press; 2016.
78. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med* 2016 12 8;375(23):2246–54. [PubMed: 27718781]
79. Polascik TJ, Pound CR, Meng MV, Partin AW, Marshall FF. Partial nephrectomy: technique, complications and pathological findings. *J Urol* 1995 10;154(4):1312–8. [PubMed: 7658526]

KEY POINTS:

1. The influx of new oncologic technologies to treat renal cell cancer (RCC) sparked interest in assessing the economics of RCC, as evident by over 50 RCC-related economic studies published between June 2010 – August 2018.
2. For localized RCC, minimally invasive procedures had comparable costs as open surgery for radical nephrectomies but had some cost advantage in partial nephrectomies.
3. For metastatic RCC, cost studies found pazopanib to have lower costs than sunitinib in the 1st-line setting whereas cost-effectiveness studies tended to favor everolimus than cabozantinib and nivolumab.

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Table 1.

Cost Effectiveness Analyses of Renal Cell Cancer

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Metastatic RCC 1st-line					
Delea et al. (2015) ^[17] USA SPM	Population: treatment-naïve mRCC pts Intervention: pazopanib (P) vs. sunitinib (S)	Perspective: U.S. health care system Parameter sources: clinical trials & literatures Cost: direct medical cost Discount rate: 3% Reference year for cost: 2013 \$ Time horizon: 37.5 months Approach: partitioned-survival analysis model, 1 wk cycle length	P vs. S Effect: LY 2.07 vs. 2.017 QALY 1.361 vs. 1.27 Cost: \$172,805 vs. \$182,439	ICER: Pazopanib Dominant; DSA: P dominant in all scenarios PSA: probability of cost-effective at WTP 100,000: 94%	- Clinical info: COMPARZ trial - Utility info: EQ-5D from PISCES trial - Costs: drugs, unit costs x nonstudy MRU in COMPARZ, dispensing & administration, supportive care, monitoring
Andahl et al. (2016) ^[18] Canada SPM	Population: Metastatic RCC consistent with the COMPARZ trial Intervention: pazopanib (P) vs. sunitinib (S)	Perspective: Health care sector Parameter sources: clinical trials & literatures Cost: direct medical Discount rate: 5% Reference year for cost: 2014 Canadian dollars Time horizon: 5 years Approach: partitioned-survival model	P vs. S Effect: LY 2.529 vs. 2.473 QALY 1.574 vs. 1.515 Cost: 100,430 vs. 109,308	ICER: C/LY: P dominant C/QALY: P dominant DSA: P dominant on all scenarios PSA: probability of cost-effective dominant in 79% of simulations	- Clinical info: COMPARZ - Utility info: EQ-5D from COMPARZ & VEG105192 trial - Costs: drugs, unit costs x nonstudy MRU in COMPARZ, dispensing & administration, supportive care, monitoring
Andahl et al. (2017) ^[19] UK SPM	Population: Metastatic RCC compatible with that of the COMPARZ trial Intervention: Pazopanib (P) vs. Sunitinib (S)	Perspective: health care sector Parameter sources: clinical trials & literatures Cost: direct medical Discount rate: 3.5% Reference year for cost: 2014 £ Time horizon: 5 years Approach: A partitioned-survival analysis model	P vs S Effect: LY 2.5784 vs. 2.5210 QALY 1.6026 vs. 1.5432 Cost: \$56,612 vs. \$57,966 examined in deterministic sensitivity analyses	ICER: C/LY: P dominant C/QALY: P dominant DSA: P dominant in almost all scenarios PSA: probability of cost-effective at WTP £20,000 (\$28,736) per QALY: 96%	- Clinical info: COMPARZ - Utility info: EQ-5D from COMPARZ & VEG105192 trial - Costs: drugs, unit costs x nonstudy MRU in COMPARZ, dispensing & administration, supportive care, monitoring
Capri et al. (2017) ^[20] Italy SPM	Population: Advanced or metastatic RCC; Intervention: pazopanib (P) vs. sunitinib (S)	Perspective: Health care sector Parameter sources: clinical trials & literatures Cost: direct medical Discount rate: 3% Reference year for cost: 2014 € Time horizon: 5 years	P vs. S Effect: LY 2.5954 vs. 2.5377 QALY 1.6125 vs. 1.5528 Cost: \$70,575 vs \$77,062	ICER: C/LY: P dominant C/QALY: P dominant DSA: P dominant in all scenarios PSA: probability cost-effective at WTP €20,000 (\$27,100): 85%	- Clinical info: COMPARZ - Utility info: EQ-5D from COMPARZ & VEG105192 trial - Costs: drugs, unit costs x nonstudy MRU in COMPARZ, dispensing & administration, supportive care, monitoring

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Calvo Aller et al. (2011) ^[22] Spain SPM	<i>Population:</i> mRCC <i>Intervention:</i> sunitinib (SUN) vs. bevacizumab/IFN α (B-IFN) vs. sorafenib (SOR)	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2008 € <i>Time horizon:</i> 10 years <i>Approach:</i> Markov mode	SUN vs. B-IFN vs. SOR <i>Effect:</i> LY 2.9 vs. 2.67 vs. 2.74 QALY 1.87 vs. 1.71 vs. 1.7 <i>Cost:</i> \$198,924 vs. \$237,925 vs. \$200,812	<i>ICER:</i> C/LY: SUN dominant C/QALY: SUN dominant OWSA: drug costs, utility values and HR were influential drivers for both SUN vs B-IFN or SUN vs SOR P5A: probability of cost-effective at WTP €50,000 (\$76,336), 75%	- SOR was not a current SoC for 1st-line CC mRCC - Clinical info: via indirect comparison using IFN α as the common comparator - Utility info: based on treatment regimen, instead of health state - Cost: MRU (by expert opinion) x unit cost
Benedict et al. (2011) ^[23] USA and Sweden SPM	<i>Population:</i> mRCC <i>Intervention:</i> sunitinib (SUN) vs. bevacizumab/IFN α (B-IFN) vs. sorafenib (SOR) (only for USA)	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2008 \$ <i>Time horizon:</i> lifetime <i>Approach:</i> Markov model	USA: SUN vs. B-IFN vs. SOR Sweden: SUN vs. B-IFN <i>Effect:</i> USA: LY 2.9 vs. 2.67 vs. 2.743 QALY 1.876 vs. 1.714 vs. 1.706 Sweden: LY 2.9 vs. 2.67 QALY 1.862 vs. 1.703 <i>Cost:</i> USA: \$482,218 vs. \$570,734 vs. \$499,942 Sweden: \$185,905 vs. \$238,222	<i>ICER:</i> C/LY: SUN dominant C/QALY: SUN dominant OWSA: results most influenced by HRs for PFS and OS and treatment costs P5A: probability of cost-effective (USA): 74 % at WTP of \$100,000 (Sweden): 99 % at WTP of SEK500,000 (~ \$76,760)	- SOR was not a current SoC for 1st-line CC mRCC - Clinical info: via indirect comparison using IFN α as the common comparator - Utility info: based on treatment regimen, instead of health state - Cost: MRU (by expert opinion) x unit cost
Wu et al. (2012) ^[24] China Not SPM	<i>Population:</i> mRCC <i>Intervention:</i> sunitinib (SUN) vs. bevacizumab plus IFN α (B-IFN) vs. IFN α + IL2	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2011 \$ <i>Time horizon:</i> lifetime <i>Approach:</i> A decision-analytic model	SUN vs. B-IFN vs. IFN vs. IL2 vs. IFN + IL2 <i>Effect:</i> LY: 2.71 vs. 2.55 vs. 2.41 vs. 2.32 vs. 2.35 QALY: 1.4 vs. 1.23 vs. 1.11 vs. 1.08 vs. 1.09 <i>Cost:</i> Without PAP: \$108,579 vs. \$202,348 vs. \$36,903 vs. \$31,045 vs. \$40,300 With PAP: \$30,493 vs. \$196,436 vs. \$29,527 vs. \$24,515 vs. \$33,149	<i>ICER:</i> C/LY 15,328 (SUN with PAP vs IL2) C/QALY: 19,224 (SUN w/ PAP vs IL2) OWSA: the PFS HR of SUN was the most influential driver (SUN w/ PAP vs IL2) P5A: SUN w/ PAP was the most cost-effective approach when WTP was over \$16,000/QALY	- Both IFN α or IL2 + IFN α were not current SoC for 1st-line mRCC - IL2 was not SoC for 1st-line non-CC mRCC - When compared to other current SoC, SUN with PAP dominates B-IFN - Clinical info: via indirect comparison using IFN α as the common comparator - Cost: drugs, exams, BSC, physician visits, and AE management
Metastatic RCC, 2nd-line treatment					
Peirou et al. (2014) ^[25] Cyprus Not SPM	<i>Population:</i> mRCC; 2nd-line (1st-line NS) <i>Intervention:</i> sorafenib (S) vs. BSC	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3.5% <i>Reference year for cost:</i> 2012 € <i>Time horizon:</i> 10 years	S vs. BSC <i>Effect:</i> LY NS QALY: 0.639 vs. 0.478 <i>Cost:</i> \$38,899 vs. \$11,990	<i>ICER:</i> C/LY NS C/QALY: \$166,946 OWSA: ICER could be as low as \$74,523/QALY if sorafenib price by patient access schemes P5A: probability of cost-effective at WTP €60,000 (\$100,000), 0%	- Clinical info: TARGET trial - Utility info: literature

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
		<i>Approach:</i> probabilistic Decision analytic Markov Model			
Peirou et al. (2014) ^[26] Cyprus Not SPM	<i>Population:</i> RCC patients in Cyprus eligible for 2nd-line treatment (1st-line NS); <i>Intervention:</i> sorafenib (S) vs. BSC	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3.5% <i>Reference year for cost:</i> 2012 € <i>Time horizon:</i> 10 years <i>Approach:</i> Markov chain Monte Carlo model	S vs. BSC <i>Effect:</i> Incremental QALY: 0.1605 <i>Cost:</i> \$27,802 vs. \$12,000	<i>ICER:</i> \$98,147/QALY if the price of sorafenib should be set at 1816 euro per package, a price notably lower compared to current price OWSA: the price of sorafenib, utility, and PFS were the most influential drivers <i>PSA:</i> ml	- A value based pricing study - Clinical info: TARGET trial - Utility info: literature
Mihajlovi et al. (2013) ^[27] Serbia Not SPM	<i>Population:</i> mRCC. 2nd-line after refractory to sunitinib <i>Intervention:</i> everolimus (E) vs. BSC	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% (cost) & 1.5% (effect) <i>Reference year for cost:</i> 2013 € <i>Time horizon:</i> lifetime <i>Approach:</i> Markov model	E vs. BSC <i>Effect:</i> LY 0.8113 vs. 0.5658 QALY 0.5804 vs. 0.3943 <i>Cost:</i> \$49,254 vs. \$1,873	<i>ICER:</i> C/LY: \$192,960 C/QALY: \$254,578 OWSA: ICER could be up to \$1,620,831/QALY at the extreme of the hazard multiplier <i>PSA:</i> probability of cost-effective at WTP €2,402 (\$35,551)/QALY (3-fold the domestic gross national product per capita): 0%	- The authors also investigate budget impact
Paz-Ares et al. (2010) ^[28] Spain SPM	<i>Population:</i> Average age 62 y/o Spanish mRCC after 1st-line IL-2 or IFNa <i>Intervention:</i> sunitinib (S) vs. BSC	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> trials & literature <i>Cost:</i> direct medical <i>Discount rate:</i> 3.5% <i>Reference year for cost:</i> 2007 € <i>Time horizon:</i> 10 years <i>Approach:</i> Markov Model	S vs. BSC <i>Effect:</i> LY: 1.84 vs. 0.53 QALY: 1.36 vs. 0.39 <i>Cost:</i> \$61,376 vs. \$3,836	<i>ICER:</i> 44,057/LY; 59,787/QALY <i>OWSA:</i> ICER most sensitive to probability of death from mRCC, utilities after progression, and cost of sunitinib, ICER could be up to \$73,353/QALY <i>PSA:</i> probability of cost-effective at WTP €45 000 (\$68,702)/QALY: 95%	- IFNa was not current SoC for 1st-line mRCC
Giuliani et al. (2018) ^[29] Italy NSPM	<i>Population:</i> mRCC pts on 2nd-line <i>Intervention:</i> nivolumab (N) vs. temsirolimus (T) vs. sorafenib (S) vs. axitinib (A) vs. everolimus (E) vs best supportive care (BSC)	<i>Perspective:</i> not specified <i>Parameter sources:</i> pivotal phase 3 clinical trials <i>Cost:</i> drugs only <i>Discount rate:</i> NS <i>Reference year for cost:</i> 2017 € <i>Time horizon:</i> during treatment <i>Approach:</i> calculated based on pts in phase 3 trials	N vs. T vs. S vs. A vs. E vs. BSC <i>Effect:</i> PFS (month): 4.6 vs. 4.3 vs. 3.9 ~ 4.7 vs. 6.7 vs. 4.4 ~ 4.9 vs. 1.9 Median OS (month) 25 vs. 12.3 vs. 16.5 ~ 16.6 vs. 15.2 vs. 14.8 ~ 19.6 vs. 14.4 <i>Cost:</i> \$33,626 vs. \$22,583 vs. \$17,458 ~ \$21,822 vs. \$31,443 vs. \$15,496 ~ \$20,661 vs. 0	Cost per week of PFS gained: \$1,291 (E vs. BSC) \$1,203 (A vs. S) \$2,951 (T vs S) \$16,206 (N vs. E) Cost per month of OS gained: \$38,740 (E vs BSC) S dominated A S dominated T \$2,401 (N vs. E)	- Clinical info: CheckMate 025, RECORD-1, AXIS, INTORSECT - Costs limited to the costs of drugs at the pharmacy of the authors' hospital - Concluded N is cost-effective even though data from four trials were analyzed separately, without performing any modeling or indirect comparison

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Edwards et al (2018) ^[30] UK NSPM	<i>Population:</i> Advanced or metastatic RCC, 2nd-line after VEGF-targeted therapy <i>Intervention:</i> best supportive care [BSC] vs. everolimus (E) vs. axitinib (A) vs. cabozantinib (C) vs. nivolumab (N)	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literature <i>Cost:</i> direct medical <i>Discount rate:</i> 3.5% <i>Reference year for cost:</i> 2015 £ <i>Time horizon:</i> lifetime (30 years) <i>Approach:</i> A partitioned survival model	BSC vs. E vs. A vs. C vs. N <i>Effect:</i> LY: 1.25 vs. 2.21 vs. 2.21 vs. 3.18 vs. 2.53 QALY: 0.75 vs. 1.31 vs. 1.31 vs. 1.87 vs. 1.6 <i>Cost:</i> \$16,778 vs. \$54,121 vs. \$69,027 vs. \$158,098 vs. \$158,462	<i>ICER:</i> C/QALY (stepwise): \$66,792 (E vs. BSC) E dominated A \$187,018 (C vs. E) C dominated N OWSA: most sensitive to parameters related to OS hazard ratio and relative dose intensity <i>PSA:</i> similar to the deterministic base case analysis - CEA finding in favor of E	- Clinical info: modelled based on CheckMate025 and derived relative treatment effectiveness through network meta-analysis - utility info: systematic review - Costs: drug acquisition and administration, disease management, AEs, subsequent treatment, terminal care, and miscellaneous - sunitinib included in the systematic review but not in the independent economic assessment
Surfay et al. (2017) ^[31] USA Not SPM	<i>Population:</i> Advanced RCC, 2nd-line (1st-line NS) <i>Intervention:</i> Nivolumab (N) vs. Everolimus (E) vs. BSC	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> trials & literature <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2016 \$ <i>Time horizon:</i> 10 years <i>Approach:</i> Markov model	N vs. E <i>Effect:</i> LY (incremental) 0.24 QALY (incremental) 0.34 <i>Cost:</i> \$103,069 vs. \$52,214	<i>ICER:</i> N vs. E \$214,143/LY \$150,213/QALY N vs. BSC \$231,879/QALY E vs. BSC \$498,813/QALY OWSA: Limiting the maximal treatment duration of N to 2 year reduced the ICER to \$124,847/QALY <i>PSA:</i> probability that N is cost-effective than E at WTP \$100,000 is 0% but grew to 90% at \$140,000/QALY	- The results of stepwise comparison was not reported but could be calculated - Clinical info: from CheckMate 025 trial & RECORD-1 trial to incorporate BSC - Utility info: from CheckMate 025 trial with modification to estimate the average utility - Cost: drug, adverse event, and administration costs
Wan et al. (2017) ^[34] China and USA Not SPM	<i>Population:</i> mRCC 2nd-line (1st-line NS); <i>Intervention:</i> nivolumab (N) vs. everolimus (E)	<i>Perspective:</i> Health care sector <i>Parameter sources:</i> clinical trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2014 \$ <i>Time horizon:</i> 20 years <i>Approach:</i> A partitioned survival model	N vs. E <i>Effect:</i> LY 2.435 vs. 2.134 QALY 1.786 vs. 1.496 <i>Cost:</i> (incremental) USA: \$48,048 China: \$6,891 (N @ \$9.02/mg)	<i>ICER:</i> USA: \$149,782/LY \$155,669/QALY China (N @ \$9.02/mg): \$22,893/LY \$23,793/QALY OWSA: costs for N was the most influential driver <i>PSA:</i> USA: probability of cost-effective at WTP 100,000/QALY: 3.1% China (N @ \$7.9/mg) probability of cost-effective at WTP \$22,785/QALY: 90%	- different drug price in USA vs China - Clinical info: from CheckMate 025 trial - Utility info: from CheckMate 025 trial with modification to estimate the average utility - Cost: drug, administration, and adverse event costs
McCrea et al (2018) ^[35] USA SPM	<i>Population:</i> previously treated advanced RCC <i>Intervention:</i> nivolumab (N) vs. everolimus (E)	<i>Perspective:</i> Health care sector – US payer <i>Parameter sources:</i> clinical trials & literature <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2017 \$ <i>Time horizon:</i> 25 years <i>Approach:</i> A 3-state (progression-free, progressive disease, and death) partitioned-survival model	N vs. E <i>Effect:</i> LY: 3.36 vs. 2.61 QALY: 2.79 vs. 2.15 <i>Cost:</i> \$197,089 vs. \$163,902	<i>ICER:</i> C/LY: \$44,576 C/QALY: \$51,714 OWSA: sensitive to survival inputs for OS and average weight of pts <i>PSA:</i> probability of cost-effective (N vs. E) at WTP \$150,000: 91.7%	- Clinical & EG-5D info: CheckMate 025 - Costs: drug acquisition and administration, monitoring, adverse events, disease management, end-of-life care

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Raphael et al (2018) ^[36] Canada NSPM	Population: mRCC; 2nd-line (1st-line antiangiogenic therapies) Intervention: nivolumab (N) vs. everolimus (E)	Perspective: Health care sector Parameter sources: clinical trials & literature Cost: direct medical Discount rate: 3% Reference year for cost: 2016 Canadian dollars Time horizon: lifetime Approach: Markov model	N vs. E Effect: LM 36.4 vs. 30.35 QALM 25.08 vs. 20.88 Cost: \$77,729 vs. \$49,003	ICER: C/QALM: \$6,845 OWSA: everolimus favored in most scenarios, only sensitive to drug cost of N and median OS PSA: probability of N being cost-effective at WTP 50,000 Canadian dollars (\$41,390)/QALY: 0%, and approached 50% at WTP 100,000 Canadian dollars (\$82,781)/QALY	- Clinical info: CheckMate-025 and statistics Canada - Utility info: EQ-5D from CheckMate-025, post-progression utility from 2 similar Canadian trials - Costs: drug-related, disease monitoring, adverse events, subsequent treatment after progression, death-related costs
Meng et al (2018) ^[37] UK SPM	Population: Advanced RCC following prior VEGFR-targeted therapy Intervention: cabozantinib (C) vs. axitinib (A) vs. everolimus (E) vs. nivolumab (N)	Perspective: National Health Service (i.e., health care sector) and personal social services in England Parameter sources: clinical trials & literature Cost: direct medical Discount rate: 3.5% Reference year for cost: 2017 £ Time horizon: 30 years Approach: partitioned-survival model	C vs. A vs. E vs. N Effect: LY: 2.26 vs. 1.78 vs. 1.78 vs. 2.08. QALY: 1.78 vs. 1.4 vs. 1.4 vs. 1.64. Cost: \$120,885 vs. \$66,736 vs. \$45,948 vs. \$130,572	ICER: C vs. N: C dominant C vs. A: C/LY: \$110,511 C/QALY: \$142,194 C vs. E: C/LY: \$152,932 C/QALY: \$197,486 OWSA: sensitive to drug costs, time horizon, and discount rate PSA: probability cost-effective (C vs. A) at WTP £100,000 (\$143,678)/QALY: 50%	- Clinical info: METEOR, CheckMate025, and AXIS trial - Direct comparison only available for C vs. N (from METEOR), other comparisons established via network meta-analysis - utility info: EQ-5D-5L from METEOR - Costs: treatment, adverse events, PFS health state costs, progressed health state costs, and terminal care - Despite having multiple comparators, the study conducted pairwise comparisons
Swallow et al (2018) ^[38] USA SPM	Population: mRCC with at least 1 prior targeted therapy Intervention: everolimus (E) vs. cabozantinib (C) vs. nivolumab (N) vs. axitinib (A)	Perspective: Health care sector – third-party payer in the US Parameter sources: clinical trials & literature Cost: direct medical Discount rate: not applied due to short time horizon Reference year for cost: 2016 \$ Time horizon: 1- and 2-year Approach: decision-analytic model built in Excel	E vs. C vs. N vs. A Effect: (mean, in month) 1-year time horizon LY: 9.9 vs. 10.6 vs. 10.7 vs. 9.7 PFS: 5.7 vs. 7.3 vs. 6 vs. 6.2 2-year time horizon: LY: 15.9 vs. 17.5 vs. 18.2 vs. 15.2 Cost: E: \$98,685 (all AEs) C: \$133,684 (only treatment-emergent AEs) N: \$114,300 (all AEs) A: \$112,388 (all AEs)	ICER: (1-year horizon) C/LY (in month): \$49,998 (C vs. E) \$24,822 (N vs. E) E dominated A C/PFS (in month): \$21,874 (C vs. E) \$66,192 (N vs. E) \$35,891 (A vs. E) OWSA: sensitive to mean OS, mean PFS, duration of therapy, and drug costs	- Clinical info: RECORD- 1, CheckMate 025, METEOR, AXIS, and literature - Costs: drug-related, AEs, monitoring, subsequent treatment within the model time horizon - analysis employing 2- year time horizon reached similar conclusion - Despite having multiple comparators, the study conducted pairwise comparisons
Casciano et al. (2011) ^[39] USA SPM	Population: mRCC after 1st-line sunitinib Intervention: everolimus (E) vs. sorafenib (S)	Perspective: Health care sector Parameter sources: trials & literature Cost: direct medical cost Discount rate: 3% Reference year for cost: 2010 \$ Time horizon: 6 years Approach: Markov Model	E vs. S Effect: LY 1.805 vs. 0.533 QALY 1.298 vs. 0.382 Cost: \$152,200 vs. \$52,295	ICER: \$78,505/LY \$109,103/QALY OWSA: ICER most sensitive to post progression mortality; ICER could be up to \$138,040/QALY PSA: probability of cost-effective at WTP \$70,000 ~ \$90,000/QALY: 15.8% ~ 98%	- Authors concluded that E was cost-effective because the ICER fell within the cost per QALY range for many other widely used oncology medicines

Study, year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Petrou et al. (2015) ⁽⁴⁰⁾ Cyprus Not SPM	Population: mRCC; 2nd-line (1st-line NS) Intervention: axitinib (A) vs. sorafenib (S)	Perspective: Health care sector Parameter sources: trials & literature Cost: direct medical cost Discount rate: 3.5% Reference year for cost: 2015 € Time horizon: 10 years Approach: Markov Model	A vs. S Effect: QALY: NS Cost: NS	ICER: \$145,936/QALY OWSA: most sensitive to utility with ICUR up to \$200,837/QALY PSA: probability of cost-effective at WTP €60,000 (\$100,000): 13% [or 70% if WTP €100,000 (\$166,667)]	- EVPI: €827,200 per year

AE: adverse event; BSC: best supportive care; CC: clear cell; DSA: deterministic sensitivity analyses; EVPI: expected value of perfect information; HR: hazard ratio; ICER: incremental cost effectiveness ratio; IFNa: interferon-alpha; IL-2: interleukin-2; info: information; LY: life-year; LM: life-month; mRCC: metastatic RCC; MRU: medical resource utilization; NMB: net monetary benefit; NS: not specified; OS: overall survival; OWSA: one-way sensitivity analysis [most influential parameters]; PAP: patient assistance program; PFS: progression free survival; PSA: probabilistic sensitivity analysis; pt: patient; QALY: quality-adjusted life year; QALM: quality-adjusted life months; RCC: renal cell carcinoma; SoC: standard of care; SEER: surveillance, epidemiology and end results; SPM: sponsored by product manufacturer; VEGFR: vascular endothelial growth factor receptor; wk: week; WTP: willingness to pay; y/o: years old

#: not reported in the original article, authors' calculation

Table 2.

Cost analyses of Renal Cell Cancer

Study & year of publication, country	Target population & intervention	Study details*	Results	Conclusion	Comments
Local stage RCC					
Camp et al. (2017) ^[42] UK SPM	Population: RCC undergoing PN Intervention: RPN vs. LPN vs. OPN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Hospital Episode Statistics data (Apr 2008 – Sep 2015) <i>Cost:</i> Costs relating to inpatient, outpatient, emergency <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2015 £ <i>Time horizon:</i> 1 years <i>Approach:</i> Database (N=4,275)	<i>Cost:</i> (mean) Complication-related cost at 90 days: RPN (N=610): \$191 LPN (N=1060): \$297 OPN (N=2605): \$471 One-year total cost: \$3,101 vs. \$3,302 vs. \$4,448	RPN was associated with fewer cost	- Rates of RPN increased from 3% in 2009 to one in seven in 2014. - GLM for covariates adjustment.
Golombos et al. (2017) ^[43] USA Not SPM	Population: Non-metastatic RCC Intervention: RRN vs. LRN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> SEER-Medicare, 2008 – 2012 <i>Cost:</i> total inpatient charges <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2017 \$ <i>Time horizon:</i> during inpatient <i>Approach:</i> database (N=815)	<i>Cost:</i> (median, propensity score matched): RRN (N=574): \$53,681 vs. LRN (N=241): \$44,161	RRN was associated with significantly higher inpatient charges	- Similar survival, 3 year overall survival 88% vs. 87.9%
Golombo et al. (2017) ^[44] USA Not SPM	Population: Non-metastatic RCC Intervention: MIRN vs. ORN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> SEER-Medicare, 2001–2012 <i>Cost:</i> Medicare payment <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2012 \$ <i>Time horizon:</i> 90 days <i>Approach:</i> database (N=12,515)	<i>Cost:</i> (median, propensity score matched): Inpatient: MIRN (N=1,776): \$16,509 ORN (N=10,739): \$16,181 30-day: \$18,194 vs. \$17,830 90-day: \$19,869 vs. \$19,047	MIRN was associated with lower morbidity and had comparable costs as ORN	- Use of MIRN increased from 8% in 2001–2004 to 21.7% in 2009–2012. - Authors advocated the oncologic efficacy of MIRN
Kim et al. (2013) ^[45] USA Not SPM	Population: RCC Intervention: ORN vs. LRN vs. OPN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Nationwide Inpatient Sample (NIS) <i>Cost:</i> in-hospital total costs (calculated from cost-to-charge ratio in NIS) <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2011 \$ <i>Time horizon:</i> in-hospital <i>Approach:</i> database (N=49,983)	<i>Cost:</i> (median, unadjusted) ORN (N=35,712): \$13,726 LRN (N=5,327): \$13,866 OPN (N=8,944): \$13,762 Adjusted, no complication \$15,655 vs. \$14,910 vs. \$14,367 Adjusted, w/ complication \$25,226 vs. \$23,214 vs. \$22,365	Although postoperative complications were associated with higher costs, these three types of surgeries had similar costs	- Investigated the relationship between costs and complications - Generalized estimating equations method to adjust for patient and hospital covariates
Kowalczyk et al. (2013) ^[46] USA Not SPM	Population: RCC, 93% stage I Intervention: SUV vs. ablation vs. MIPN vs. OPN vs. MIRN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> SEER-Medicare, 2005 – 2007 <i>Cost:</i> Medicare payment <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2007 \$ <i>Time horizon:</i> 3 months <i>Approach:</i> database (N=1,682)	<i>Cost:</i> (mean) SUR (N=42): \$3,941 ablation (N=211): \$14,515 MIPN (N=160): \$21,251 OPN (n=330): \$22,999 MIRN (n=535): \$20,815 ORN (n=404): \$24,105	Treatment cost was lowest by SUR, followed by ablation then nephrectomy	- Mortality rate was highest for ORN and lowest for MIPN, but not reported for SUR - Use of ablation increased from 6.1% in 2005 to 15.4% in 2007
Larcher et al.	Population: T1a unilateral RCC	<i>Perspective:</i> health care sector	<i>Cost:</i> (median, propensity score matched)	LTA is associated with lower expenditure	- Similar 30 day mortality but lower morbidity for LTA

Study & year of publication, country	Target population & intervention	Study details*	Results	Conclusion	Comments
(2017) ^[47] USA Not SPM	<i>Intervention:</i> LTA vs. PN	<i>Parameter sources:</i> SEER-Medicare, 2000 – 2009 <i>Cost:</i> Medicare payment <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2014 \$ <i>Time horizon:</i> 1 year <i>Approach:</i> database (N=2,471)	LTA (N=510): \$16,609 PN (N=1,961): \$21,306		
Bahler et al (2018) ^[48] USA NSPM	<i>Population:</i> adult (< 18) underwent PN for localized RCC <i>Intervention:</i> OPN vs. LPN vs. RPN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Nationwide Inpatient Sample database, 2009 - 2012 <i>Cost:</i> hospital cost only, not including physician fees <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2010/2011 <i>Time horizon:</i> hospital stay for surgery <i>Approach:</i> Database (N=56,512)	<i>Cost:</i> Median unadjusted OPN: \$15,063 (N=32,664) LPN: \$15,015 (N=3,498) RPN: \$16,728 (N=20,350) Adjusted (compared to OPN) LPN: -\$207 (P=0.736) RPN: \$1,022 (P=0.004)	Analysis stratified by year showed that the difference in cost between RPN and OPN decreased over time and became statistically insignificant by 2012	- total number of PN semiannually increased 93% from 2009 to 2012; RPN accounted for 80% of the increase - % PN performed as robotic-assisted increased from 20% in 2009 to 50% in 2012 - Multiple linear regression used for covariates adjustment - RCC identified via ICD-9 codes
Chang et al (2018) ^[49] Taiwan NSPM	<i>Population:</i> RCC pts underwent radical or partial nephrectomy <i>Intervention:</i> OPN vs. MIPN vs. OPN vs. MIPN	<i>Perspective:</i> health care sector <i>Parameter sources:</i> National Health Insurance Research Database of Taiwan, 2006 – 2012 <i>Cost:</i> direct medical cost <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2009 \$ <i>Time horizon:</i> hospital stay for surgery <i>Approach:</i> Database (N=3,172)	<i>Cost:</i> ORN: \$4,091 (N=1,847) MIPN: \$3,880 (N=625) OPN: \$3,384 (N=519) MIPN: \$3,654 (N=181)	No statistically significant difference in cost between open and minimally invasive surgeries, nor between RN and PN	- Although information on covariates was available, study only reported unadjusted analyses - RCC identified via ICD-9 code (189.0: malignant neoplasm of kidney, except pelvis)
mRCC, non-pharmaceutical					
Takagi et al. (2014) ^[50] Japan Not SPM	<i>Population:</i> mRCC received cytoreductive nephrectomy <i>Intervention:</i> laparoscopic (L) vs. open surgery (O)	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Japanese Diagnosis Procedure Combination database, 2007 – 2012 <i>Cost:</i> total inpatient cost <i>Discount:</i> NA <i>Reference year for cost:</i> 2014, reported in \$ <i>Time horizon:</i> in-hospital <i>Approach:</i> database (N=1,074)	<i>Cost:</i> L (N=244) was 3.4% higher than O (N=830) in multivariate analysis	Laparoscopic surgery costed more than open surgery	- Primary goal was to examine perioperative outcomes of cytoreductive nephrectomy by clinical T stage. - Generalized estimation equation for covariate adjustment
mRCC 1st line treatment					
Villa et al. (2013) ^[51] Spain SPM	<i>Population:</i> Advanced RCC with favorable or intermediate risk in Spain in 2013 <i>Intervention:</i>	<i>Perspective:</i> health care sector <i>Parameter sources:</i> literature <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2013 € <i>Time horizon:</i> 1 years <i>Approach:</i> Markov model	<i>Cost:</i> (annual per patient) P: \$50,981 S: \$62,063	The introduction of pazopanib results in cost savings	- Budget impact analysis also performed, with cost saving \$10,378,763

Study & year of publication, country	Target population & intervention	Study details*	Results	Conclusion	Comments
	pazopanib (P) vs. sunitinib (S)				
Hansen et al. (2015) ^[52] USA SPM	<i>Population:</i> Advance RCC <i>Intervention:</i> pazopanib (P) vs. sunitinib (S)	<i>Perspective:</i> health care sector <i>sources:</i> resource utilization from COMPARZ, unit costs from MarketScan Databases <i>Cost:</i> medical/ambulatory and pharmacy services <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2013 \$ <i>Time horizon:</i> same as the observational period in COMPARZ. <i>Approach:</i> database (N=906)	<i>Cost:</i> (annual per patient) P (N=454): \$89,963 S (N=452): \$97,143	Healthcare costs were lower for pazopanib	- Post-hoc secondary analysis on patient-reported health care resource utilization in the COMPARZ trial. - The highest 1% cases were excluded in cost analyses
MacLean et al. (2016) ^[53] USA SPM	<i>Population:</i> RCC mostly metastatic <i>Intervention:</i> pazopanib (P) vs. sunitinib (S)	<i>Perspective:</i> health care sector <i>Parameter sources:</i> MarketScan Research Databases, 2009 – 2013 <i>Cost:</i> all-cause total costs <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2016 \$ <i>Time horizon:</i> 1 years <i>Approach:</i> Database (N=792)	<i>Cost:</i> (mean) Daily, unadjusted, without substitution: P (N=183): \$181 S (N=609): \$273 1 year mean, unadjusted - Age < 65: \$126,153 vs > 65: \$134,417 (P=0.34) - Age > 65: \$86,849 vs. \$96,025 (P=0.24) Adjusted results were similar to those found in unadjusted results	The effect of substituting days supply values was demonstrated	- GLM for covariate adjustment
Vogelzang et al. (2017) ^[54] USA SPM	<i>Population:</i> Elderly advanced RCC <i>Intervention:</i> pazopanib (P) vs. sunitinib (S)	<i>Perspective:</i> health care sector <i>sources:</i> Medicare database plus Part D linkage, 2006 – 2014 <i>Cost:</i> Medicare payment <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2015 \$ <i>Time horizon:</i> a month <i>Approach:</i> Database (N=1,711)	<i>Cost:</i> (mean per month, propensity score matched) P (N=526): \$9,411 S (N=1,185): \$11,082	Pazopanib treatment was associated with lower healthcare costs	- Higher survival with pazopanib (hazard ratio 0.83, 95% confidence interval 0.72–0.97; p = 0.016)
Racsa et al. (2015) ^[55] USA Not SPM	<i>Population:</i> Advanced RCC <i>Intervention:</i> pazopanib (P) vs. sunitinib (S)	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Humana Research Database, 2009 – 2012 <i>Cost:</i> All costs included plan- and patient-paid amounts <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2015 \$ <i>Time horizon:</i> 1 year <i>Approach:</i> database (N=319)	<i>Cost:</i> (annual mean) P (N=102): \$68,552 S (N=217): \$81,524	Sunitinib treatment trended towards higher index medication and total healthcare costs	- No statistical significant difference in survival - Multivariate generalized linear model was used of covariates adjustment
Vogelzang et al (2018) ^[56] USA SPM	<i>Population:</i> advanced RCC pts 65, with sunitinib or pazopanib as first targeted therapy <i>Intervention:</i>	<i>Perspective:</i> health care sector <i>Parameter sources:</i> 100% Medicare claims linked to Part D, Oct 1, 2009 - Jan 1, 2014 <i>Cost:</i> direct medical quantified as Medicare paid amount <i>Discount rate:</i> NA	<i>Cost:</i> [mean cost among 522 matched pairs] all-cause total monthly health care costs: P: \$9,072 vs. S: \$11,623 all-cause total monthly medical costs: P: \$4,246 vs. \$6,257 all-	For 1st-line oral targeted therapies, P was associated with lower all-cause healthcare costs but also lower compliance than S	- cohort identified via kidney cancer ICD-9 (189.0x, 189.1x) + secondary neoplasm code (196.xx-199.xx) - Propensity score matched- costs: total all-cause health care costs = total

Study & year of publication, country	Target population & intervention	Study details*	Results	Conclusion	Comments
	pazopanib (P) vs. sunitinib (S)	<i>Reference year for cost:</i> 2015 \$ <i>Time horizon:</i> time on treatment <i>Approach:</i> Database (N=1,711 before matching; 526 on P and 1,185 on S)	cause total monthly pharmacy costs: P: \$4,826 vs. \$5,366		all-cause medical + all-cause + pharmacy costs
Ravasio et al. (2011) ^[57] Italy SPM	<i>Population:</i> mRCC <i>Intervention:</i> Bevacizumab + IFN α (B-IFN) vs. sunitinib (S)	<i>Perspective:</i> health care sector (Italian National Health Service) <i>Parameter sources:</i> literatures <i>Cost:</i> direct medical <i>Discount rate:</i> NS <i>Reference year for cost:</i> 2010 € <i>Time horizon:</i> 1 years <i>Approach:</i> model, indirect comparison (due to a lack of head-to-head trial)	<i>Cost:</i> cost savings (B-IFN vs. S) \$3,045 per patient (for IFN 9 MIU)	Bevacizumab + IFN α was a cost-saving alternative to sunitinib.	- Cost-minimization analysis as authors assumed similar efficacy between B-IFN and S - Cost difference mainly driven by the terms of risk-sharing agreement between Italian NHS and the manufacturer of B and S
Soerensen et al (2015) ^[58] Denmark Not SPM	<i>Population:</i> Danish mRCC <i>Intervention:</i> Targeted therapy (TT) vs. immunotherapy (I)	<i>Perspective:</i> both societal and health care sector <i>Parameter sources:</i> Danish National Patient Registry, 2002–2009 <i>Cost:</i> all inpatient and outpatient payment <i>Discount rate:</i> omitted (due to short median overall survival ~ 14 mo.) <i>Reference year for cost:</i> 2011 € <i>Time horizon:</i> life time <i>Approach:</i> Database (N=631)	<i>Cost</i> (per patient per year) drug cost: I (N=183) (2006–2009 cohort): \$2,047 TT (N=256) (2006–2009 cohort): \$10,566 Total health care costs: I: (N=192) (2002–2005 cohort, all I): \$29,182 Mixture of I & TT (N=439) (2006–2009 cohort): \$28,994	Implementation of TT was associated with change in health care pattern without significant change in total cost	- Danish National Patient Registry had information on all inpatient and outpatient contacts. - No statistically significant difference in indirect cost between periods (2002–2005 vs. 2006–2009) - GLM for covariates adjustment
mRCC 2nd-line treatment					
Pal et al. (2016) ^[59] USA SPM	<i>Population:</i> mRCC, 2nd-line after sunitinib, sorafenib, or pazopanib <i>Intervention:</i> axitinib (A) vs. everolimus €	<i>Perspective:</i> health care sector <i>Parameter sources:</i> medical record retrospective review, 2012–2013 <i>Cost:</i> total drug costs 2014 \$ <i>Discount rate:</i> NS <i>Reference year for cost:</i> 2014 \$ <i>Time horizon:</i> a month <i>Approach:</i> database (N=452)	<i>Cost</i> (adjusted mean per month of PFS) A (N=127): \$13,613 E (N=325): \$11,615	Drug costs were significantly higher with axitinib	- GLM for covariate adjustment - Only considered drug acquisition costs
Perrin et al. (2015) ^[60] USA SPM	<i>Population:</i> Advanced RCC 2nd-line after failing sunitinib <i>Intervention:</i> axitinib (A) vs. everolimus €	<i>Perspective:</i> health care sector <i>Parameter sources:</i> trials & literatures <i>Cost:</i> direct medical <i>Discount rate:</i> 3% <i>Reference year for cost:</i> 2014 \$ <i>Time horizon:</i> lifetime <i>Approach:</i> Markov model	<i>Cost</i> (lifetime): Base case analysis A: \$127,990 E: \$113,811 Average from probabilistic analysis: A: \$128,775 E: \$114,779	- Everolimus likely leads to lower lifetime costs - One way sensitivity analysis: incremental cost could be as low as \$3,257 if drug intensity changed	- Assumed OS of everolimus and axitinib was equivalent - Difference in lifetime cost was primarily driven by higher drug costs of A - Mean months of drug supply: A 7.14 vs. E 6.16
mRCC, all lines of therapy					
Sou et al. (2017) ^[61] Canada Not SPM	<i>Population:</i> mRCC <i>Intervention:</i> Various dose/Schedule modifications of sunitinib	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Saskatchewan Cancer Agency, 2006–2013 <i>Cost:</i> total drug cost <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2017	<i>Cost</i> (monthly average) standard intermittent dosing (SID): (N=59): \$4,914 modified intermittent schedule (MIS) (N=9): N/A intermittent dosing (MID)	Several adjusted-dose sunitinib regimens (MIS, MID, and MSD) were associated significantly lower costs when compared to SID	- Dose adjustment was associated with better survival - Analysis of variance was used to compare costs

Study & year of publication, country	Target population & intervention	Study details*	Results	Conclusion	Comments
Geynisman et al (2015) ^[62] USA Not SPM	<i>Population:</i> < 65 y/o mRCC <i>Intervention:</i> modern IV treatment (MIV) (i.e., bevacizumab or temsirolimus) vs. IV treatment vs. oral treatment	Canadian dollars <i>Time horizon:</i> time on treatment <i>Approach:</i> Database (N=161)	(N=60): \$3,283 modified intermittent schedule and dosing (MSD) (N=25): \$3,478 continuous dosing (CD) (N=8): N/A <i>Cost:</i> (annual total cost) MIV (N=122): \$183,146 IV (N=314, including the 122 MIV): \$150,812 Oral (N=645): \$140,122	Total costs were highest for patients with MIV as first-line therapy <i>Sensitivity analysis:</i> similar cost trends	- Median annual drug cost increased from \$12,811 in 2004 to \$76,765 in 2010
Shi et al (2018) ^[63] China SPM	<i>Population:</i> mRCC pts with sequential treatment <i>Intervention:</i> sunitinib + axitinib (SA) vs. sunitinib + everolimus (SE) vs. sunitinib + sorafenib (SS)	<i>Perspective:</i> health care sector, Chinese payer <i>Parameter sources:</i> trials published in literature <i>Cost:</i> direct medical <i>Discount rate:</i> NS <i>Reference year for cost:</i> 2016 ¥. <i>Time horizon:</i> during treatment <i>Approach:</i> Excel-based model for cost calculation	<i>Cost:</i> mean, per patient per month SA: \$4,321 SE: \$4,342 SS: \$5,830	SA yielded largest cost savings Scenario analysis –1: lowest cost sequence with sorafenib as 1st-line is sorafenib+axitinib Scenario analysis –2: lowest cost sequence when adding 3rd-line is SA+ everolimus	- Chinese Society of Clinical Oncology recommended sunitinib or sorafenib as 1st-line, axitinib or everolimus as 2nd-line, and everolimus or sorafenib as 3rd-line - Cost: treatment (accounted for drug discount programs), and adverse events - SA had higher AE costs than 1st-line sorafenib regimens
Maroun et al (2018) ^[64] France SPM	<i>Population:</i> mRCC pts received 1st- line targeted therapy <i>Intervention:</i> sunitinib (SU) sorafenib (SO) pazopanib (P) bevacizumab (B) everolimus (E) temsirolimus (T)	<i>Perspective:</i> health care sector <i>Parameter sources:</i> IQVIA-RWD Oncology Cross-Sectional Survey Data, French data Oct 2005 – Sept 2015 <i>Cost:</i> drug costs only <i>Discount rate:</i> NA <i>Reference year for cost:</i> 2010 € <i>Time horizon:</i> during treatment <i>Approach:</i> Database (N=1,331)	<i>Cost:</i> mean €/day (treatment duration) 1st vs. 2nd vs. 3rd-line SU: \$224 (99) vs. \$240 (61) vs. \$235 (70) SO: \$72 (43) vs. \$118 (73) vs. \$126 (87) P: \$115 (88) vs. NA vs. NA B: \$2,249 (6) vs. \$2,417 (7) vs. \$2,759 (9) E: \$238 (86) vs. \$211 (118) vs. \$216 (74) T: \$750 (9) vs. \$811 (9) vs. \$819 (11) axitinib: NA vs. \$199 (58) vs. \$211 (93)	This study reported per-day drug cost by targeted therapy agent and line of therapy in French patients with mRCC without formal cost comparison	- IQVIA, RWD is a pt-level cancer treatment database in Europe collected from physicians - Primary goal of the study was to describe real-world treatment pattern and outcomes. Cost was not the main focus - sunitinib was the most common 1st-line treatment for mRCC

*: “reference year for cost” represents the reference year and currency used in the original paper

CC: clear cell; GLM: generalized linear model; IV: intravenous; LTA: local tumor ablation; LPN: laparoscopic RN; MI: minimally invasive; MIU: million IU; NS: not specified; mRCC: metastatic RCC; NSPM: not SPM; OPN: open PN; ORN: open RN; PN: partial nephrectomy; RCC: renal cell carcinoma; RN: radical nephrectomy; RPN: robotic RN; SPM: sponsored by product manufacturer; SUR: surveillance; y/o: years old

#: including those mostly treated in the 1st-line setting

Table 3.

Cost of Illness Studies of Renal Cell Cancer

Study & year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
RCC, all stages					
Hollenbeak et al. (2011) ^[61] USA Not SPM	Population: Elderly with newly diagnosed RCC	<i>Perspective:</i> health care sector (Medicare) <i>Parameter sources:</i> SEER- Medicare, 1995 – 2002 <i>Cost:</i> Medicare payment <i>Discount:</i> NA <i>Reference year for cost:</i> 2005 \$ <i>Time horizon:</i> 1 and 5 year <i>Approach:</i> database: (N=14,814)	RCC (N=4,938) vs. non-cancer control (N=9,876) <i>Cost:</i> (mean) cumulative 1 year cost: RCC: \$49,540 vs. Control: \$13,620 Cumulative 5-year cost: RCC: \$162,948 vs. Control: \$92,317 Adjusted differences: 1-year: \$32,855 5-year: \$30,849	- Newly diagnosed RCC is associated with significant economic burden - Factors associated with higher RCC costs included older age, black race, comorbidity, disease stage, and receipt of chemo or surgery plus radiation	- RCC and comparison group were 1:2 matched - Applied propensity score matching to construct non-cancer control - Statistical analyses accounted for censored cost
mRCC					
Ballali et al. (2013) ^[70] Italy Not SPM	Population: mRCC patients in public hospitals in Veneto region who received sunitinib as 1st-line treatment and sorafenib as 2nd-line (n=357)	<i>Perspective:</i> health care sector <i>Parameter sources:</i> literatures and data derived from institutional pharmacological database <i>Cost:</i> direct medical <i>Discount:</i> NS <i>Reference year for cost:</i> 2013 € <i>Time horizon:</i> 3 years <i>Approach:</i> Markov model	<i>Cost:</i> (population aggregate) 1st-line sunitinib 1 year: \$4,971,977 3 year: \$5,230,776 1st-line sunitinib & 2nd sorafenib 1 year: \$5,238,080 3 year: \$5,623,280	The major cost-driver was sunitinib as 1st-line treatment	- Veneto is a region in Italy with a population of 4.8 million - Appeared to have only captured drug costs
Maroun et al. (2017) ^[71] France Not SPM	Population: treatment naïve mRCC patients who received a first-line targeted therapy	<i>Perspective:</i> health care sector (NHI in France) <i>Parameter sources:</i> NHI claims data for Ile-de-France region, 2012–2014 <i>Cost:</i> all cause health care cost, reported as per patient per month (PPPM) <i>Reference year for cost:</i> 2016 € <i>Time horizon:</i> varied by patients, from the index date to the end of follow-up period <i>Approach:</i> database (N=327)	<i>Cost:</i> (mean, PPPM) Total: \$6,944 Pre-progression: \$7,007 Post progression: \$6,936	- Targeted oral therapies accounted for 53% of the overall monthly costs - Higher hospitalization costs in the post-progression period may be driven by increasing use of targeted IV drugs after progression	- 18% of French resided in the Ile de France region - mRCC identified via ICD-10 codes - targeted therapies included sorafenib, temsirolimus, pazopanib, bevacizumab, everolimus, sunitinib, and axitinib - Study also reported progression free and overall survival
Maroun et al. (2016) ^[72] France Not SPM	Population: adult patients hospitalized for mRCC treatment not specified	<i>Perspective:</i> health care sector (French NHI) <i>Parameter sources:</i> French national hospitals database, 2008 – 2013 <i>Cost:</i> hospital cost <i>Discount:</i> NA <i>Reference year for cost:</i> 2015 € <i>Time horizon:</i> one year <i>Approach:</i> database (N=15,752, accounting for 102,613 hospital stays related to mRCC)	<i>Cost:</i> (mean annual per capita cost of hospital management) \$11,293 (2008 cohort) \$12,829 (2012 cohort)	- In-hospital costs of managing mRCC were mainly driven by expensive drugs - Observed a sustained decrease in the number of patients receiving “expensive drug” over time; the decrease might be driven by increasing use of oral anticancer drugs	- Focused on in-hospital economic burden - Costs were based on published DRG tariffs, which may underestimate costs for private hospitals - Expensive drug list only captured targeted IV agents, not targeted oral mRCC identified via ICD-10 codes

Study & year of publication, country	Target population & intervention	Study details	Results	Conclusion	Comments
Purmonen et al (2010) ^[73] Finland Not SPM	Population: mRCC receiving 1st-line interferon-alpha (IFNα)	<i>Perspective:</i> societal <i>Parameter sources:</i> patient data from 3 university hospitals (2006 – 2007) & literature <i>Cost:</i> direct medical + productivity loss <i>Discount:</i> NS <i>Reference year for cost:</i> 2008 <i>€Time horizon:</i> life time <i>Approach:</i> database (N=83) + modeling for future costs and budget impact of sunitinib	<i>Cost</i> (mean lifetime treatment cost) \$41,253 Budget impact analysis: predicted 5-year budget of IFNα-based treatment was \$20M - \$33M, increased to \$16 M - \$51 M if sunitinib was added to first-line	mRCC poses significant economic burden for Finland, and burden is expected to increase due to the aging demographics as well as the adoption of targeted therapies and the associated survival benefit	- IFNα only was not a current standard of care for mRCC - Costs based on resource use data of 47 patients - Travel costs not included - Medication accounted for 60% of treatment cost during active treatment phase with IFNα and reduced to 6% after active treatment
Li et al (2018) ^[74] USA NSPM	Population: elderly fee-for service Medicare beneficiaries with mRCC	<i>Perspective:</i> health care sector <i>Parameter sources:</i> Medicare 2011 – 2013 Chronic Data Warehouse, linked with Part D plan and formulary characteristics files <i>Cost:</i> out-of-pocket drugs costs <i>Reference year for cost:</i> 2012 # \$ <i>Time horizon:</i> per month <i>Approach:</i> database: (N=1,721)	<i>Cost</i> (mean out-of-pocket for targeted therapies covered by Part D, per month) With low-income subsidies (LIS) (N=322): \$8 Without LIS (N=1,399): \$3,208	High cost-sharing was associated with higher out of pocket cost, and lower rates of initiating targeted oral therapies under Medicare Part D	- Primary focus was initiation of targeted therapy, only provided rough cost estimates - Incident cohort of mRCC identified via claims-based algorithms, not cancer registry
mRCC: AE					
Hagiwara et al. (2013) ^[75] USA SPM	Population: mRCC receiving 1st-line targeted therapies, specifically, sunitinib, sorafenib, bevacizumab or pazopanib;	<i>Perspective:</i> health care sector <i>Parameter sources:</i> PharMetrics Patient-Centric Database, 2003 – 2009 <i>Cost:</i> total health care costs, excluding targeted therapies costs <i>Reference year for cost:</i> 2013 \$ <i>Time horizon:</i> within 30 days of an AE <i>Approach:</i> database (N=303)	<i>Cost</i> (mean) Unadjusted: with AE (N=194): \$13,615 without AE (N=109): \$4,550 Adjusted: \$12,716 higher for patients with any AE	- Targeted therapies were associated with substantial AE costs - 64% of working age mRCC patients who treated with targeted therapies had 1 encounter indicative of AE	- Applied claims-based algorithm to exclude transitional cell carcinoma - Sample size for the w/ and w/o AE groups in the "Any AE" column in the cost table did not add up to the total sample size - GLM (one for each AE) for covariates adjustment.
Hagiwara et al. (2013) ^[76] USA SPM	Population: elderly mRCC receiving 1st-line targeted therapies (sunitinib, sorafenib, bevacizumab, and pazopanib	<i>Perspective:</i> health care sector <i>Parameter sources:</i> SEER- Medicare, 2007 <i>Cost:</i> total direct health care costs, excluding targeted therapies costs <i>Reference year for cost:</i> 2013 \$ <i>Time horizon:</i> within 30 days of an AE <i>Approach:</i> database: (N=881)	<i>Cost</i> (mean) Unadjusted: with AE (N=526): \$15,590 without AE (N=355): \$2,100 Adjusted: \$13,875 higher for patients with any AE	- Costs of adverse events are substantial higher in elderly mRCC patients receiving targeted therapies - 60% of elderly mRCC patients had 1 encounter indicative of AE	- Total costs = Medicare payment + patient co-insurance and liability - Sample size for the w/ and w/o AE groups in the "Any AE" column in the cost table did not add up to the total sample size - GLM for covariate adjustment

AE: adverse events; CC: clear cell; GLM: generalized linear model; mRCC: metastatic RCC; NHI: National Health Insurance; NA: not applicable; NS: not specified; RCC: renal cell carcinoma; SPM: sponsored by product manufacturer

#: inferred from the year of data (2011 – 2013) as the reference year for cost was not specified in the paper.

Table 4:

Number of Studies Not Meeting CHEERS Checklist Items

Item No	Description of Checklist Item	CEA (N=21)	Cost (N=23)	COI (N=8)	Total (N=52)	%
1	Title	0	6	0	6	12
2	Abstract	0	0	0	0	0
3	Background and objectives	0	0	0	0	0
4	Target population and subgroups	0	0	0	0	0
5	Setting and location	0	0	0	0	0
6	Study perspective	1	0	0	1	2
7	Comparators	0	0	0	0	0
8	Time horizon	0	0	0	0	0
9	Discount rate	1	2	2	5	10
10	Choice of health outcomes	0	0	0	0	0
11	Measurement of effectiveness	0	0	0	0	0
12	Measurement and valuation of preference based outcomes	3	0	0	3	6
13	Estimating resources and costs	0	0	0	0	0
14	Currency, price date, and conversion	1	8	2	11	21
15	Choice of model	1	0	0	1	2
16	Assumptions	1	0	0	1	2
17	Analytical methods	0	0	0	0	0
18	Study parameters	0	0	0	0	0
19	Incremental costs and outcomes	0	0	0	0	0
20	Characterizing uncertainty	1	2	2	5	10
21	Characterizing heterogeneity	20	16	5	41	79
22	Study findings, limitations, generalizability, and current knowledge	0	1	0	1	2
23	Source of funding	2	2	0	4	8
24	Conflicts of interest	0	0	0	0	0

Table 5.

Overall Characteristics of Studies Reviewed

		CEA	Cost	COI	TOTAL
Country	USA	7	14	4	25
	Canada	2	1	0	3
	UK	3	1	0	4
	Italy	2	1	1	4
	Spain	2	1	0	3
	Sweden	1	0	0	1
	Cyprus	3	0	0	3
	Serbia	1	0	0	1
	France	0	1	2	3
	Finland	0	0	1	1
	Denmark	0	1	0	1
	China	2	1	0	3
	Japan	0	1	0	1
	Taiwan	0	1	0	1
Sponsorship	SPM	11	11	3	25
	Not SPM	10	12	5	27
Cancer Stage	Non-metastatic	0	8	0	8
	Metastatic	21	15	7	43
	NS	0	0	1	1
Perspective	Health sector	20	22	7	49
	Societal	0	1	1	2
	NS	1	0	0	1
Approach	Model	21	4	1	26
	Database	0	19	6	25
	Mixed	0	0	1	1

Note: some studies including more than one country; SPM: sponsored by product manufacture; NS: not specified