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The clinical and economic burden of metastatic renal cell carcinoma in Canada in real-world setting.

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Thesis to the graduate students department

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August 2019

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Abstract

Aim: The management of metastatic renal cell carcinoma (mRCC) has changed significantly in the past decade with the scientific advancement in the field of pharmacotherapy, the search for optimal timing of surgery and different ablation methods. In parallel, the economic burden of mRCC has grown with increased incidence and costly treatments. This research program aimed: 1) to evaluate effectiveness and costs of targeted therapy (sunitinib and pazopanib) in first-line setting in clear cell mRCC patients; 2) to develop a Markov model with Monte-Carlo simulations in order to assess the cost-utility of sunitinib vs. pazopanib in patients who have mRCC in first-line setting from the Canadian healthcare system perspective and 3) to evaluate the impact of metastasectomy on clinical outcomes in mRCC patients using real-world data from Canadian academic hospitals.

For the first objective of this research program, the Canadian Kidney Cancer information system (CKCis), a pan-Canadian database, was used to identify prospectively collected mRCC patients' data between January 2011 and December 2017. Survival curves (Kaplan-Meier, conditional survival and direct adjusted survival curves) were used to estimate the unadjusted and adjusted overall survival (OS) by treatment. Unit treatment cost was taken from the Régie d'assurance Maladie du Québec (RAMQ) list of medications to estimate the cost by line of treatment and the total cost of targeted therapy for the management of mRCC patients. We included 475 patients receiving sunitinib or pazopanib in the first-line setting. Patients were mostly treated with sunitinib (81%), and 19% of patients were treated with pazopanib. The adjusted OS with sunitinib was 32 months compared to 21 months with pazopanib (p=0.01). The total average first-line cost of treatment with sunitinib and pazopanib was $94,232 (95%CI: $74,059 - $114,169) and $70,000 (95%CI: $32,942 -$107,993), respectively.

For the second objective, a Markov model with Monte-Carlo microsimulations was developed to estimate the clinical and economic outcomes of patients treated in first-line with sunitinib vs. pazopanib over a 5-year period. Transition probabilities were calculated using the effectiveness results from the first objective. The costs of therapies, disease progression, and management of adverse events were included in the model in Canadian dollars. The difference in quality-adjusted life year (QALY) was 0.54 in favour of sunitinib with an incremental cost-utility ratio (ICUR) of $67,227/QALY for sunitinib vs. pazopanib. The difference in life years gained (LYG) was 1.21 (33.51 vs. 19.03 months), and the incremental cost-effectiveness ratio (ICER) was $30,002/LYG.

For the third objective, patients were stratified depending if they were managed with a complete or incomplete metastasectomy or no metastasectomy. A total of 417 patients had a complete (273 patients) and incomplete (144 patients) metastasectomy, respectively. At 12 months, 98.7%, 87.1% and 77.7% of patients were alive in the complete metastasectomy, incomplete metastasectomy and no metastasectomy group, respectively ($p<0.001$). After matching, patients who underwent complete metastasectomy had a longer overall survival (HR: 0.41, 95%CI:0.30-0.56) compared to patients who did not undergo metastasectomy, but this benefit was not shown in patients undergoing incomplete metastasectomy (HR: 0.95, 95%CI: 0.71-1.28) vs. non-metastasectomy patients.

In conclusion, using the CKCis database, we have assessed the real-life utilization of resources such as pharmacotherapy and surgical management as well as their respective outcome on mRCC patients in Canada. Also, our cost-utility analysis is the first economic analysis based on real-world evidence, and positions well the clinical values found in our results with regards to the economic value of targeted therapy.

Keywords: renal cancer, metastatic, metastasectomy, sunitinib, pazopanib, systemic therapy, Markov Model with Monte-Carlo microsimulations, costs of renal cell carcinoma, cost-effectiveness, economic burden

Résumé

Contexte: La prise en charge du carcinome à cellules rénales métastatique (CCRm) a fortement évolué au cours de la dernière décennie avec les avancées scientifiques dans le domaine de la pharmacothérapie, la recherche sur le moment propice pour les résections chirurgicales et les différentes méthodes d'ablation. Parallèlement, le fardeau économique du CCRm a augmenté avec l'incidence accrue et les traitements coûteux. Ce programme de recherche vise: 1) à évaluer l'efficacité d'un traitement ciblé (sunitinib et pazopanib) en première ligne chez des patients atteints d'un CCRm à cellules claires et estimer les coûts reliés au traitement ciblé; 2) développer un modèle de Markov avec des simulations de Monte-Carlo afin d'évaluer l'utilité économique du sunitinib par rapport au pazopanib chez les patients ayant un CCRm en première intention sur une période de 5 ans; et 3) évaluer l'impact de la métastasectomie sur les résultats cliniques chez les patients atteints de CCRm à l'aide de données réelles provenant d'hôpitaux universitaires Canadiens.

Pour le premier objectif de ce programme de recherche, le système d'information sur le cancer du rein canadien (CKCis), une base de données panCanadienne, a été utilisé pour identifier les données des patients avec CCRm collectées prospectivement entre Janvier 2011 et Aril 2019. Les courbes de survie (Kaplan-Meier et courbes de survie ajustées) ont été utilisées pour estimer la survie globale non ajustée et ajustée par type de traitement utilisé. Le coût unitaire de traitement est tiré de la liste des médicaments de la Régie d'assurance maladie du Québec (RAMQ) pour estimer le coût par traitement et le coût total pour la prise en charge des patients atteints du CCRm. Nous avons inclus 475 patients recevant le sunitinib (81%)

ou le pazopanib (19%) en première intention. La survie globale ajustée avec le sunitinib était de 32 mois contre 21 mois avec le pazopanib (p=0,01). Le coût médian total du traitement par le sunitinib et le pazopanib était de 56 476$ (IQR: 23 738 $ - 130 447$) et de 46 251$ (IQR: 28 167$ - 91 394$), respectivement.

Pour le second objectif, un modèle de Markov avec des microsimulations de Monte-Carlo a été développé pour estimer les résultats cliniques et économiques des patients traités en première intention par sunitinib ou pazopanib. Les probabilités de transition ont été estimées en utilisant les résultats d'efficacité du premier objectif. Le coût des thérapies, la progression de la maladie et la gestion des événements indésirables ont été inclus dans le modèle en dollars canadiens. La différence dans l'année de vie ajustée sur la qualité (QALY) était de 0,54 en faveur du sunitinib avec un ratio cout-utilité incrémental de 67,227 $ / QALY pour le sunitinib contre le pazopanib. La différence entre les années de vie gagnées était de 1,21 (33,51 vs 19,03 mois) et le rapport cout-efficacité incrémental était de 30,002 $ par année de vie gagnée.

Pour le troisième objectif, les patients étaient stratifiés selon qu'ils étaient pris en charge par une métastasectomie complète ou incomplète ou sans métastasectomie. Un total de 417 patients ont eu une métastasectomie complète (273 patients) et incomplète (144 patients) respectivement. À 12 mois, 98,7%, 87,1% et 77,7% des patients étaient vivants dans le groupe métastasectomie complète, métastasectomie incomplète et pas de métastasectomie, respectivement (p<0,001). Lorsque les patients ont été appariés, le fait d'avoir une métastasectomie était encore un prédicteur de la survie (HR: 0.41; 95%CI : 0.30 - 0.56; p<0.001).

En conclusion, la base de données CKCis a démontrée l'utilisation réelle de ressources comme la pharmacothérapie et la gestion chirurgicale ainsi que leurs résultats respectifs chez les patients atteints de CCRm au Canada. En outre, notre analyse coût-utilité est la première analyse économique fondée sur des données probantes et positionne bien les valeurs cliniques trouvées dans nos résultats en ce qui concerne les thérapies ciblées de première ligne.

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Signs and abbreviations list

AS	Active Surveillance
ASIR	Age-Standardized Incidence Rate
ALP	Alkaline phosphatase
CA	Cryoablation
ccRCC	clear cell Renal Cell Carcinoma
CDC	Collecting Duct Carcinoma
CSS	Cancer Specific Survival
CI	Confidence Interval
CT	Computed Tomography
EGFR	Epithelial Growth Factor Receptor
ECOG	Eastern Cooperative Oncology Group
HPRC	Hereditary Papillary Renal Carcinoma
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
ICUR	Incremental Cost-Utility Ratio
IMDC	International Metastatic renal cell carcinoma Database Consortium
LDH	Lactose Dehydrogenase
KPS	Karnofsky Performance Status
mRCC	metastatic Renal Cell Carcinoma
mTOR	mammalian Target of Rapamycin
MET	Mesenchymal Epithelial Transition
MRI	Magnetic Resonance Imaging
NSS	Nephron-Sparing Surgery
OS	Overall Survival

OR	Odds Ratio
PN	Partial Nephrectomy
pCODR	panCanadian Oncology Drug Review
PFS	Progression Free Survival
QALY	Quality-Adjusted Life Years
RAMQ	Régie de l'Assurance Maladie du Québec
RFA	Radio Frequency Ablation
RN	Radical Nephrectomy
RR	Relative Risk
RCC	Renal Cell Carcinoma
TNM	Tumour, Lymph Nodes and Metastasis
TKI	Tyrosine Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor
WTP	Willigness to Pay

To,

Nada Hamdar & Mohamad Nazha

Acknowledgments

I would like to start by thanking my supervisor, Alice Dragomir for her continuous support and guidance throughout one of the most fruitful experiences in my life. These past years have been instrumental in my career development. Thank you for widening my experience through research, teaching, presentations and collaboration. I thank Dr. Simon Tanguay for his support and guidance. Thank you for taking the time and attention to follow my research projects with great interest.

I would like to acknowledge the support of the Canadian Centre for Applied Research in Cancer Control (ARCC) for awarding me with the 2017 studentship award.

I would like to thank all the clinicians with whom I had the opportunity and honor to interact while doing my PhD; Dr. Wassim Kassouf, Dr. Armen Aprikian, Dr. Marie Vanhuyse, Dr. Sergio Faria and Dr. Luis Souhami. I thank my committee members, Dr. Jacques Lapointe, Dr. Maria Petropavlovskaya, Dr. Eric Latimer, Mrs. Nathalie Letarte for their support and guidance. Their advice and recommendations were instrumental in my research development.

I would like to thank my colleagues, Halima Lahcène, Noémie Prévost, Jason Hu, Samer Trabulsi, Ivan Yanev for their collegiality and friendship during these years.

My thanks and gratitude to my managers at Sanofi Canada, Manon Leduc and Franca Mancino, for supporting me througth this journey. Your support and encouragement were instrumental during these years.

Finally, I would like to thank my family. Thank you to my brother and father who were by my side along the way. Thank you to my life partner, Karim Haroun, who supported me during my last academic step and fully encouraged me on this journey. Thank you for your love and patience.

Author contribution

There are three manuscripts in this thesis. The authors' contributions have been described in specific manuscript, as part of the standard formatting required by the journals. The contributions of the co-authors of each manuscript are summarized below.

Utilization of targeted therapy in metastatic renal cell carcinoma patients: clinical and economic impact in Canadian real-life setting.

Study conception and design: Nazha S, Dragomir A, Tanguay S.

Data acquisition and analysis: Nazha S, Dragomir A.

Data interpretation: Nazha S, Dragomir A, Tanguay S.

Drafting of manuscript: Nazha S.

Critical revisions: Dragomir A, Kapoor A, Jewett M, Kollmannsberger C, Wood L, Bjarnason G, Heng D, Soulières D, Reaume N, Basappa N, Lévesque E, Tanguay S.

Cost-Utility of sunitinib vs. pazopanib in metastastic renal cell carcinoma in Canada using real-world evidence.

Study conception and design: Nazha S, Dragomir A, Tanguay S.

Data acquisition and analysis: Nazha S, Dragomir A.

Data interpretation: Nazha S, Dragomir A, Tanguay S.

Drafting of manuscript: Nazha S.

Critical revisions: Dragomir A, Kapoor A, Jewett M, Kollmannsberger C, Wood L, Bjarnason G, Heng D, Soulières D, Reaume N, Basappa N, Lévesque E, Tanguay S.

Outcomes of metastasectomy in metastatic renal cell carcinoma (mRCC) patients: The Canadian Kidney Cancer information system experience.

Study conception and design: Nazha S, Dragomir A, Tanguay S.

Data acquisition and analysis: Nazha S, Dragomir A.

Data interpretation: Nazha S, Dragomir A, Tanguay S.

Drafting of manuscript: Nazha S.

Critical revisions: Dragomir A, Finelli A, Hansen A, Kollmannsberger C, Wood L, Rendon R, So A, Heng D, Soulières D, Pouliot F, Basappa N, Kapoor A, Tanguay S.

Statement of originality

As one of the leading countries in health technology assessment, Canada is rich in its research in health outcomes and health economics. Economic analyses are usually found in a variety of therapeutic areas to understand the economic burden and to assess cost-effectiveness / cost-utility of new treatments. Our cost-effectiveness study is a concrete example of evidence supporting decision-making in the healthcare system as we looked at the two most utilized targeted treatments in the management of mRCC. In parallel, an important part of this is represented by assessing clinical outcomes as demonstrated in our first and third objective, which looked into the effectiveness and cost of sunitinib and pazopanib as well as the clinical outcomes after metastasectomy in mRCC patients.

In regard to renal cell carcinoma (RCC), the relatively low incidence of this disease translates into very few economic and research outcomes analyses pertaining to this cancer in Canada. This being said, our research program identifies a gap in the Canadian literature and presents remarkable and valuable evidence to Canadian physicians, patients, healthcare institutions, and governments. As a matter of fact, this doctoral thesis makes notable contributions to the evidence in health outcomes and pharmacoeconomics for the management of metastatic renal cell carcinoma (mRCC) and the related cost of pharmacotherapy. In fact, our research demonstrates the clinical outcomes of mRCC patients based on pharmacotherapy and surgical management in Canada, as well as the associated health economics.

Besides, several methodological contributions are worth being mentioned. First, the usage of real-world data is very relevant to the current healthcare environment as it depicts a better understanding of the utilization of treatments in oncology. We are very fortunate in Canada to have a comprehensive registry including RCC patients across the country. Our database, which includes over 9,000 patients since 2011, is the foundation of many publications in the field of kidney cancer and a robust source of evidence for the comprehension of the disease. Second, our economic model integrates microsimulation that overcomes memory less assumptions and allows for more accurate economic analysis taking patient's characteristics into consideration, based on real-world evidence. Third, patient matching and adjusted survival curves were used to reduce bias due to confounding variables, which is found in observational datasets.

Overall, our research programs include many innovative methodologies as well as new evidence which will advance our knowledge in the field of mRCC and its management.

Chapter 1: Introduction

This chapter provides an overview of the kidney, its primary functions within the human body and its diseases, whether benign or malignant. The risk factors, clinical manifestations and epidemiology of RCC are summarized in this section.

1.1 Overview of the kidney

The kidney is defined as a pair of bean-shaped organs in the back part of the abdomen cavity. The kidney is divided into two main parts; the cortex and the medulla. The medulla is separated by segments of the cortex, called the columns of Berlin (Figure 1). Each kidney is a network of millions of small tubes called nephrons that are made up of tubule and a corpuscle. Tubules are responsible for collecting the waste materials and chemicals, and corpuscles filter the blood through tiny blood vessels. The weight of a kidney is on average 150g in male and 135g in female. The dimensions of kidneys are 10 to 12 cm vertically and 5 to 7 cm transversally.(1, 2) The kidney is an essential organ of the human body for maintaining normal human physiologic functions. In fact, the role of the kidney is to keep electrolyte balance and fluid, it controls blood pressure by producing renin and it affects the production of red blood cells by producing erythropoietin. Also, it provides calcitriol to help the colon absorb calcium. On a daily basis, the kidneys filter about 113 to 142 liters of blood to produce about 0.9 to 1.8 liters of urine, composed of wastes and extra fluid. (1)

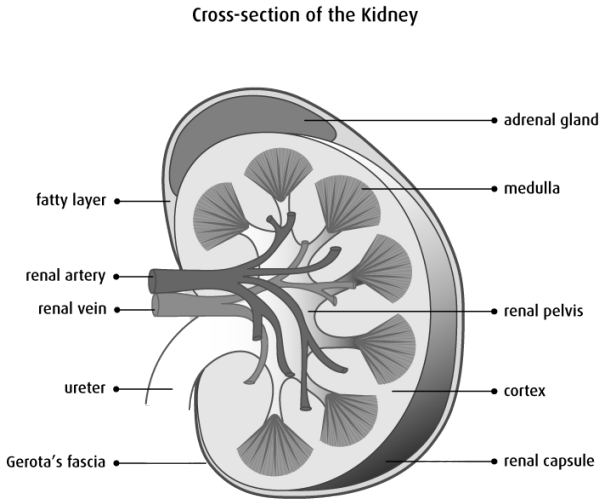


Figure 1: Morphology of the Kidney. Adapted from Canadian Cancer Society(3)

1.2 Kidney neoplasms

Kidney neoplasms can be classified differently by malignant, benign, or inflammatory or by their radiographic appearance (simple cystic, complex cystic, fatty tumours). In the following section, different neoplasms will be classified as benign and malignant and summarized on their prognosis and respective treatment options. (1)

1.2.1 Benign neoplasm

Many renal neoplasms are defined as being benign with a heterogeneous group of sub-neoplasms. Benign masses are usually diagnosed with imaging studies such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) to assess whether a renal lesion is benign or malignant before a therapeutic decision is made.(4, 5) However, the vast majority of benign renal lesions are diagnosed only after definitive therapy such as surgical intervention through partial or radical nephrectomy, where a biopsy would be conducted in order to confirm the neoplasm. Some clinical criteria are commonly seen in benign neoplasms such as small masses, older age and female sex.(6)

Adenoma

Histologically, renal adenomas appear as small, well-circumscribed lesions characterized by uniform basophilic or eosinophilic cells arranged as tubulopapillary growth.(7) The incidence of renal adenomas increases with age and being a male. These tumours also have been associated with an acquired renal cystic disease that results in end-stage renal failure.(8) The overwhelming majority of renal adenomas remain asymptomatic, as they are undetectable radiographically due to their small size. Size of the neoplasm has historically been utilized to differentiate renal adenoma from more malignant neoplasms of the kidney such as papillary RCC. (9)

Given its similar molecular presentation to papillary RCC, many studies have identified links between the incidence of adenoma and papillary RCC. As a matter of fact, Brunelli *et al.* demonstrated that renal adenomas shared similar cytogenetic profiles to papillary RCC, such as trisomy of chromosomes 7 and 17, thus suggesting a biologic link between the two neoplasms.(10, 11) In parallel, Wang *et al.* examined 542 nephrectomy specimens obtained over 8 years in order to identify morphologic characteristics linked to adenomas. Seven percent demonstrated evidence of renal adenoma and of these, 47% were associated with a concomitant papillary RCC. (12)

Oncocytoma

Renal oncocytoma is the most common benign tumour that appears as an enhancing renal mass on cross-sectional imaging and is presumed to be RCC until surgical excision. In over 32 % of cases, patients have a concomitant diagnosis of RCC and oncocytomas.(9, 13) Oncocytoma accounts for 3 to 7% of all kidney tumours and the most common genetic abnormality is loss of chromosome 1p.(14) Oncocytoma typically appears on CT or MRI as

a homogeneous, well-circumscribed solid mass containing a central scar. However, these features are not sufficiently specific to exclude RCC.(7, 9)

The incidence of oncocytoma is higher in older patients with a small renal mass as opposed to younger patients.(15) Within the younger population, females are found to have 2-fold higher rates of incidence compared to men.(8, 15)

Angiomyolipoma

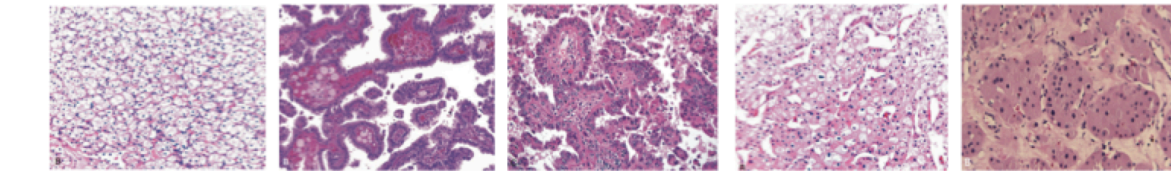
Angiomyolipoma accounts for less than 10% of renal tumours and is a benign neoplasm consisting of thick-walled aneurysmal vessels, smooth muscle and varying levels of mature adipose tissue.(16, 17) The tumour strongly expresses estrogen receptor-β as well as androgen receptor, is predominantly found in females and is rare before puberty, suggesting a potential hormonal influence.(18)

These tumours are most often sporadic but can also be associated with the autosomal dominant tuberous sclerosis complex (TSC). In fact, 20% to 30% of angiomyolipomas are in patients with TSC, and approximately 50% of patients with TSC develop angiomyolipomas. Patients with TSC also develop renal cysts and may be at higher risk of developing RCC.(18, 19)

Renal angiomyolipoma is linked to other clinical complications such as the Wunderlich syndrome, or massive retroperitoneal hemorrhage. These events represents the most significant complication as it is reported in up to 10% of patients and could be associated with significant morbidity and potential mortality if not promptly treated.(18) One of the key features of angiomyolipoma is the peripheral fat found in radiographic imaging, which makes it the only benign neoplasm to be easily identified with cross-sectional imaging. (19)

1.2.2 Malignant neoplasms

Malignant neoplams can be stratified as renal cell carcinoma (which is the most prevalent type), wilms tumour, sarcomas, urothelium based carcinomas, renal lymphoma and many more. Almost all kidney cancers first appear in the lining of tubules in the kidney. The following section describes the different types of renal cell carcinoma as this thesis focuses on this particular subtype of kidney cancer. Figure 2 presents the different histology of RCC subtypes.



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence (%)	75%	5%	10%	5%	5%

Figure 2: Histologic presentation of RCC subtypes. Adapted from Campbell et al.(1)

Clear Cell RCC (ccRCC)

The most common type of RCC is clear cell, representing 70-80% of all RCCs. The main differentiation point of clear cell histology is the vascularization of the tumours and the clear or eosinophilic cytoplasm. In addition, alteration of chromosome 3 and VHL mutations are common in clear cell RCC, which is found in over 80% of sporadic cases. Patients with clear cell RCC have worse prognosis than patients with non-clear cell RCC, such as papillary or chromophobe.(20) However, most patients responding to cytokine therapies had clear cell histology, which led to the selection of this population for further studies.(21)

The discovery of molecular pathway such as the VHL mutation, which disables HIF-1-alpha degradation and drives transcription of hypoxia associated genes including VEGF and PDGF, led to the development of treatments targeting the VEGF and PDGF receptors in order to

decrease the tumours activity and metastasis.(22, 23) At the moment, most approved targeted treatments in RCC are indicated in clear cell only, except temsirolimus which can be used in non-clear cell patients.

Papillary RCC (pRCC)

Papillary RCC is the second most common type of RCC after clear cell, representing 10% to 15% of all RCCs.(24) The main characteristic of papillary RCC is the presence of basophilic or eosinophilic cells arranged in papillary or tubular configuration.(25)

Papillary RCC is characterized by trisomy for chromosomes 7 and 17 as well as abnormalities on chromosomes 1, 12, 16 and 20. It is more commonly found in patients with end-stage renal failure and acquired renal cystic disease. Papillary RCC is stratified in two subtypes. In fact, Type 1 papillary RCC consists of small basophilic cells, which expresses cytokeratin 7. Type 2 is considered the most aggressive variants with eosinophilic cells and abundant granular cytoplasm. The suggested split between type 1 and 2 is about 75% and 25%, respectively.(26, 27)

Some cases of pRCC are hereditary and have specific hereditary syndromes such as hereditary papillary renal carcinoma (HRPC).(26) It is an autosomal dominant syndrome with high probability of developing cancer and has been associated with oncogenic activation of the mesenchymal epithelial transition (MET), which is mainly seen in type 1 pRCC.(28)

The second most common syndrome, hereditary leiomyomatosis renal cell cancer (HLRCC), is associated with cutaneous and uterine leiomyomatomas and is seen in approximately 20% of cases with pRCC, mostly associated with type 2 pRCC.(29)

Current targeted therapies have not been sufficiently studied in pRCC.However, new treatments targeting different pathways are being evaluated for pRCC such as the MET and the epithelial growth factor receptor (EGFR).(24)

Chromophobe RCC

Chromophobe RCC is a subtype of RCC that appears to be derived from the cortical portion of the collecting duct and represents less than 5% of all RCCs.(30)

Many chromosomes losses are related to the chromophobe subtype such as 1, 2, 6, 10, 13, 17 and 21. In parallel, other studies demonstrated the increased incidence of tumour factors such as TP53 mutations or an upregulated expression of the c-KIT oncogene in chromophobe RCC.(31, 32)

The prognostic of patients with chromophobe feature has been described as good with more than 90% of patients being cancer free for 5 or more years after treatment. However, many publications have distinguished the prognosis of chromophobe patients with sarcomatoid features, as this feature has been associated with worst prognosis, similarly to the other RCC subtypes.(33) More recently, targeted therapy such as sunitinib and sorafenib were assessed in chromophobe patients and found a median PFS of 10.6 months and an overall response rate of 23% in these patients. (34, 35) At the moment, these therapies are not approved by Health Canada for chromophobe RCC.

Collecting Duct Carcinoma (CDC)

Collecting duct is considered to be derived from the collecting duct of the kidney and represents less than 1% of all RCC and has a poor prognostic in the majority of patients.(36) CDC is considered as a very aggressive type of RCC with a histological heterogeneity, which

can overlap with high grade papillary tumours and urothelial carcinomas.(37) Hence, clinical outcome of CDC patients is poor with 66% dying within 2 years after diagnosis.(38)

The median survival has been estimated to be around 22 months after nephrectomy.(39) The treatment of collecting duct has been noted in studies involving cytotoxic chemotherapy and bevacizumab. In fact, a phase 2 study with 23 patients showed a median OS of 10.5 months, but when adding bevacizumab to the chemotherapy, it increased to 28 months.(38, 40) This combination is not approved for CDC patients as this point in time.

1.3 Prevalence and incidence of RCC

The epidemiology of RCC had not been studied extensively in the last decades as a repercussion of the low incidence of this cancer compared to other malignancies. The following section presents the noted trends in incidence and mortality related to RCC in Canada as well as in different countries.

1.3.1 Canadian epidemiology

The incidence of kidney cancer has been increasing at an annual rate of 3% in Canada since 1990. The number of kidney cancer cases in 1990 was estimated to be 2,530 compared to 6,600 in 2017 representing an increase of 260% in the last 27 years.(41) Figure 3 presents the annual incidence of RCC in Canada. (41)

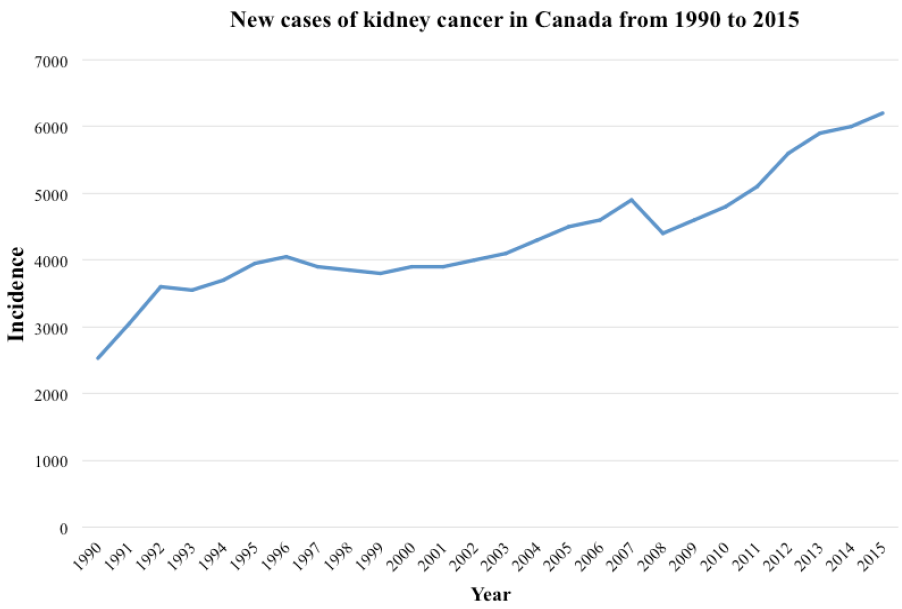


Figure 3: Incidence of kidney cancer in Canada from 1991-2015

In parallel, a Canadian publication in 1997 found the incidence rate between 1969/71 and 1989/91 to be growing from 6.37/100,00 to 10.46/100,00 respectively.(42)

From 1986 to 2007, the age-standardized incidence rate (ASIR) per 100,000 rose from 13.4 to 17.9 in males and 7.7 to 10.3 in females in Canada.(43) The ASIR is two times higher among men than women, and represents a 1.9% annual increase in men and 1.4% in women over this period for RCC patients. Provincial ASIR are generally found to be higher in eastern provinces (28.9/100,000 in New Brunswick) compared to western provinces (11.0/100,000 in British Columbia), in men. In women, the highest provincial ASIR is found in Nova Scotia (13.5/100,000) and the lowest in British Columbia (5.2/100,000).(43) Figure 4 presents the repartition of RCC ASIR by province by sex. (43)

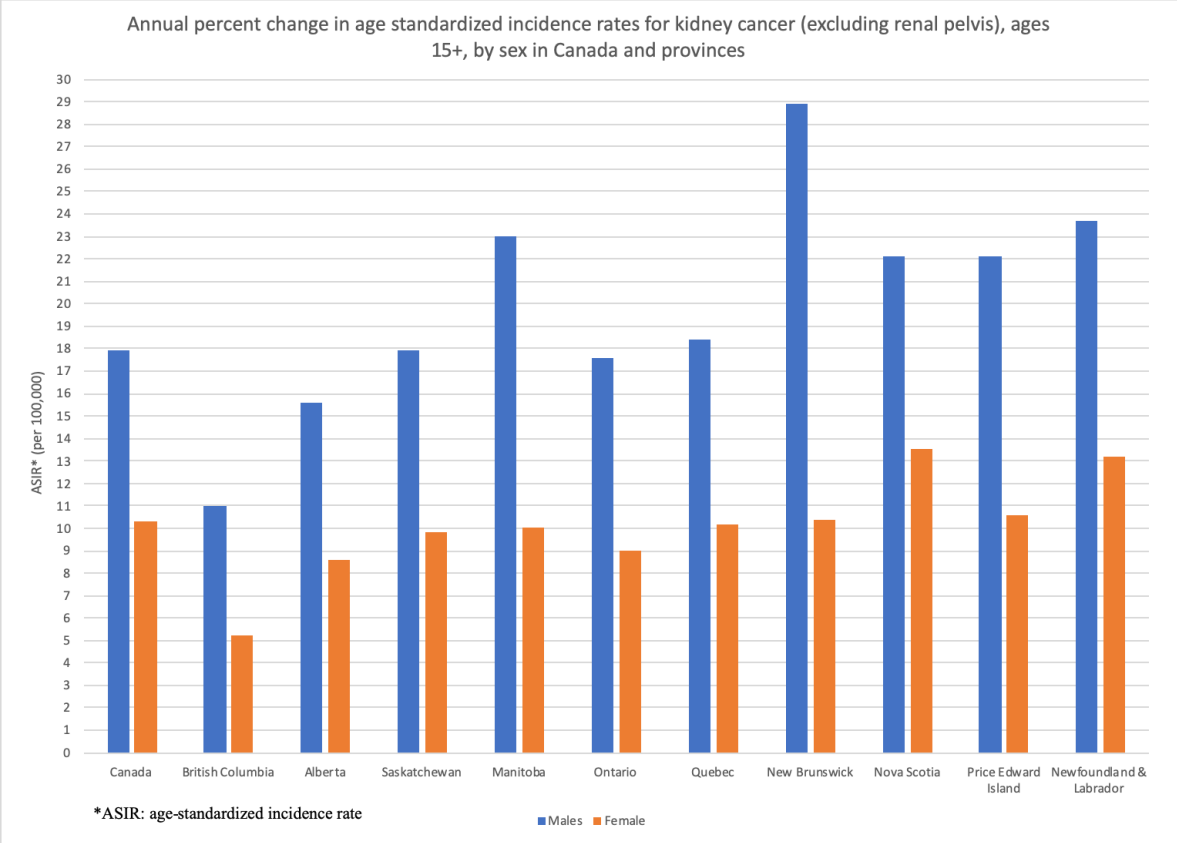


Figure 4: Repartition of RCC by ASIR in each Canadian province by sex.

The age-standardized five-year relative survival ratio (RSR) has increased by 9% from 1992 to 2008, going from 65% (1992-1996) to 71% (2004-2008) in Canada.(43) In general, mortality in RCC has declined across all age groups, with the strongest decline among patients aged 15-44 years mainly due to early detection. However, an increase was seen in male patients aged over 75 years old (0.7% annually). (43) To conclude, kidney cancer incidence in Canada has been rising in the past decades, which is clearly documented by the Canadian statistics and follows similar trend as the rest of the world, which will be presented in the next section.

1.3.2 Global epidemiology

Kidney cancer is the 14th most common cancer in the world with a global ASIR of 4/100,000 people per year in 2008.(44) Many publications underlined the increase in incidence of renal cell carcinoma over the last 3 decades internationally. As such, the incidence tends to be higher in northern Europe compared to the south Asian countries such as China, India and Japan.(45) The highest incidence rate is found in Czech Republic (22.1/100,000) and the lowest in Thailand and India (1.9/100,000).(46) In 2008, the number of new cases of kidney cancer in the world was estimated to be 273,518.(47)

In France, the estimated number of new cases annually was 11,573 in 2012, representing 3% of all cancers.(48) In the United States, the rate increased from 10.6/100,000 in 2001 to 12.4/100,000 in 2010. In Ireland, the age-adjusted incidence of RCC per 100,000 person-year increased from 5.2 in 1994 to 6.8 in 2005, an annual change of +3.4%.(49) The most predominant increase in incidence was observed in Latin American populations, where annual increases of over 3% were observed in males and female.(46)

The increase in incidence of renal cell carcinoma seems to be related to specific group of patients such as patients with localized disease. In the United States, a case-control study completed interviews with 1,136 patients where the proportion of asymptomatic cases increased from 35% to 50% between 2002 and 2007 ($p<0.001$).(50) Another study in the United States noted a similar trend in the annual percent change (APC) from 1975 to 2009.

The APC for localized disease was +4.55% (95%CI: +4.34- +4.76) compared to +0.88% (95%CI: +0.60 - +1.15) and +0.09% (95%CI: -0.19 - +0.36) in regional and distant disease, respectively.

The repartition of the prevalence does not seem to be homogenous around the globe. In fact, the prevalence of RCC is more than double in studies from Europe and North America than in Asia: 0.17% (95%CI: 0.09-0.27) versus 0.06% (95%CI: 0.03-0.09), respectively.(51)

The global mortality rate from kidney cancer was estimated to be 72,019 in 2008, with a global age-standardized mortality rate of 2.2 per 100,000 people per year.(44) Kidney cancer mortality rates have remained stable in the United States in recent decades. The annual percentage change between 1975 and 1994 was 1%, which then decreased by –0.6% from 2008 to 2010.(47) In contrast, the overall mortality rate for kidney cancer in Europe peaked at 3.5 per 100,000 from 1990 through 1994, and declined to 3 per 100,000 from 2000 to 2004.(52) To conclude, the epidemiology of kidney cancer reveals the increase of incidental cases over time, mainly due to earlier diagnosis and use of routine imaging procedures and the clear distinction found between genders, which is still not fully understood.

1.4 Risk factors

The establishment of risk factors related to RCC has not been extensively studied. However, some biological or epidemiological studies have looked into several potential risks, which are described in the following section such as cigarette smoking, hereditary RCC (such as the Von Hippel-Lindau disease), hypertension and diuretics.

Cigarette smoking

Cigarette smoking is an established risk factor for kidney cancer, particularly renal cell carcinoma (RCC). An increased risk of developing RCC is present in both current and former smokers, with heavy smokers having the highest incidence rate. Former smokers were defined by a self-reported questionnaire indicating time from cessation to surgery greater that 1 year. Compared with nonsmokers, current and former smokers have a 1.6 and 1.5-fold increased relative risk of advanced RCC, respectively.(53) Furthermore, ever-smoking men have a greater overall estimate for RCC than in ever-smoking women. Notably, ever-smoking men have an overall relative risk of RCC of 1.50 compared to that of 1.27 for ever-smoking women.(54) Results from a meta-analysis of 24 studies indicate that ever-smokers are 38% more likely to develop RCC compared to lifetime never smokers.(54) Among smokers, the increased likelihood of advanced disease is associated with higher intensity, greater smoking duration, and greater cumulative exposure.(53) A decreased risk of developing RCC is seen with smoking cessation; with longer times of cessation shown to reduce the odds of the advanced disease.(53, 55) To date, little data is available on the association between smoking and RCC biology, such that concrete evidence cannot explain the biological mechanisms behind smoking and RCC.(53)

Hereditary Papillary RCC

Hereditary Papillary renal carcinoma (HPRC) is a genetic condition that increases the risk of type 1 papillary renal cell carcinoma in affected individuals.(25, 56) Those with HPRC present an increased risk of developing kidney tumours. Currently, no other types of

correlated diseases or health problems, both cancerous and noncancerous, have been related to HPRC.(25) Further, the exact occurrence rate of this hereditary condition is unknown; however, one study identified HPRC with a cancer frequency of 19%.(25) Due to the slow-growing nature of papillary renal carcinomas, most cases of HPRC will appear either until later stages of life (at the age of 50-70 years) or at autopsy.(57) In addition, by the age of 80 years, the majority of patients with hereditary papillary renal carcinoma (approximately 90%) will develop RCC. (57)

HPRC is caused by a germline mutation of the c-*MET* gene. Notably, *MET* is a gene that codes for a tyrosine kinase receptor that binds the hepatocyte growth factor and is expressed in cells of epithelial origin. This binding action of its ligand to *MET* receptor is responsible for cell growth, survival and apoptosis inhibition. (25, 56)

Von Hippel-Lindau (VHL)

Von Hippel-Lindau (VHL) disease is an autosomal dominant condition that affects 1 in 36,000 live births in the Caucasian population.(58, 59) It is a hereditary illness that occurs with the inheritance of a mutated germline copy of the VHL gene passed from the affected parent.(59) Notably, the VHL gene that may harbor molecular alterations is a tumour suppressor gene located on 3p25, which involved in cell cycle regulation, regulation of hypoxia-inducible genes and fibronectin assembly in the extracellular matrix, thus having a significant relationship with tumour proliferation.(60) More apparent clinical indications of the disease, including both benign and malignant tumours as well as renal cysts, cerebellar,

spinal, brainstem and retinal hemangioblastoma, occurs between 18 and 30 years of age. (58, 60)

Notably, hereditary renal cell carcinoma (RCC) is significantly and commonly associated with VHL disease such that it is estimated to occur in 24 to 45% of patients with VHL disease at a mean age of 39 years.(61) Further, the relationship between clear cell RCC (ccRCC), BMI and the VHL disease was observed in a cohort study.(62) An increase per 1 kg/m^2 BMI for VHL mutation patients corresponded to an increase in ccRCC risk (HR: 1.09; 95%CI: 1.02 – 1.16) (62). As obesity is among the most important risk factor for RCC, the risk associated to the combination of both major risk factors should have significant importance. Nevertheless, RCC was a central cause of death; with a majority of patients suffering from VHL disease will eventually develop RCC if they live long enough.(59, 63) However, if RCC is detected early enough, routine surveillance can decrease morbidity and mortality among those with VHL disease.(59) Regardless, studies have revealed that the recurrence rate VHL-associated RCC patient is up to 85% at 10 years after nephron-sparing surgery (NSS).(61)

Other types of hereditary syndromes related to RCC , but less prevalent, are the Birt-Hogg-Dubé syndrome, BAP1 mutant disease, PTEN hamartoma syndrome and hereditary leiomyomatosis.(64)

Hypertension

The risk of kidney cancer, in particular RCC, is increased among patients with hypertension, thus those who exceed a blood pressure of 140/90 mm Hg.(65) Sufficient evidence demonstrates that long-term hypertension and the use of antihypertensive treatments (AHT), both independently and jointly, contribute to a significant increase in the relative risk of renal

cancer.(66) Many studies classified blood pressures, both systolic and diastolic pressures independently, into four categories each. Each category was selected on the basis of the respective definition of both normal and high blood pressure: <120 mmHg, 120–139 mmHg, 140–159 mmHg, and >160 mmHg for systolic blood pressure and <80 mmHg, 80–89 mmHg, 90–99 mmHg, and >100 mmHg for diastolic blood pressure.(65)

The European Prospective Investigation into Cancer and Nutrition (EPIC), an ongoing multicenter prospective cohort study, identified the relative risk associated with hypertension independently and including patients with use of any AHT (n=296,638). Among patients who never used AHT, the relative risk was 2.42 (95%CI: 1.35 - 4.33) for systolic pressure and 2.22 (95%CI: 1.22 - 4.04) for diastolic pressure, for the comparison of the highest versus the lowest category of blood pressure. Notably, the risk of high systolic blood pressure and kidney cancer was more significant than for high diastolic blood pressure. Also, use of such AHT correlated to an increase in RCC with a relative risk of 1.53 (95%CI: 1.12 - 2.09). However, it is difficult to assess the effect and risk of elevated blood pressure level and antihypertensive medication, since the study was based on hypertension diagnosis and its link to antihypertensive drug use.(65) Further analysis in this field would be needed to better understand the effect of different antihypertension medications and the different patient profiles treated for hypertension.

Moreover, the risk of renal cancer increases significantly with age, high systolic blood pressure, body mass index and smoking.(67) Further analysis and studies are required to analyze the pathological relationship between kidney cancer and hypertension, including a concrete explanation behind the biological mechanisms.

Diuretics/Phenacetin

The risk of renal cell carcinoma (RCC) is significantly increased with the use of phenacetin. Notably, the International Agency for Research on Cancer classified the use of phenacetin as a human carcinogen in 1987 after sufficient evidence proved its association with kidney cancer.(68) Regular use of analgesics (phenacetin), consisting of its usage for at least twice a week for 1 month or longer, showed a statistically significant increase in the risk of RCC in both men and women (OR= 1.6, 95%CI: 1.4 - 1.9).(68) Further, in a population-based-control study of kidney cancer with a population comprising of 489 cases of RCC and 147 cases of renal pelvic cancer diagnosed in 1989 and 1990, the collective use of phenacetin and acetylsalicyclic acid (ASA) has been established as a concrete risk factor for kidney cancer.(69) Although the relative risk (RR) of CaRP was significantly higher in women (RR= 17.7; 95%CI: 8.4 - 37.1) than in men (RR= 4.0; 95%CI: 1.3 - 13.0), the overall RR adjusted for both genders was found to be 12.2% (95%CI: 6.8 - 22.2) for the use of phenacetin/(ASA) compound analgesics. (69)

Further, an epidemiological study suggests that there is both a direct and indirect carcinogenic effect of phenacetin. In fact, the direct effect comes from the drug itself and its metabolites and the indirect effect comes through causation of renal papillary necrosis, which acts as a local promoter of urothelial carcinogenesis. (69, 70)

Moreover, several studies suggested that diuretics are possibly linked to a small increase in the risk of RCC, more significant among women. The associated risk between RCC and prescription diuretics in women was statistically significant such that after adjusting for

hypertension, smoking, and obesity, the odds ratio (OR) corresponded to 2.9 (95%CI: 1.7 - 4.7). In men, however, the risk and association were not established. Further, the precise biological mechanisms behind the risk were also not found.

Obesity

Excess body weight, commonly expressed in those with a body-mass index (BMI) greater than 25, is associated with the greater risk of renal cancer than normal weight people. (72) Compared to the normal weight category with a BMI between 18.5 and 24.9, the relative risk (RR) of RCC was 1.28 (95%CI: 1.24 - 1.33) and 1.77 (95%CI: 1.68 - 1.87) for the overweight (pre-obese) and obese grouping, respectively.(73) In fact, the risk of renal cancer increases with each unit increase in BMI and varies between sex and race. According to results from a cohort study, the risk of RCC for men and women increased by 4% (RR: 1.04; 95%CI: 1.03 - 1.05) and 5% (RR: 1.05; 95%CI: 1.04 - 1.06), respectively, for each BMI increment of 1 kg/m^2(73). Further, a correlation between BMI and renal cancer was noticed among whites with a HR of 1.07 (95%CI: 1.03 - 1.12). This association was not observed among blacks with a HR of 0.99 (95%CI: 0.96 - 1.03). (74)

Moreover, kidney cancer and obesity can be associated through several biological hormone mechanisms. With increasing BMI, the human body is prone to elevated levels of free insulin like growth factor-I (IGF-I) and to fasting serum; both may contribute to the growth and proliferation of renal cancer.(75) Patients with diabetes also have an increased risk of kidney cancer due to their elevated levels of plasma insulin levels. (76, 77) Increased hormone levels

in obese patients may influence renal cell proliferation and growth by direct endocrine receptor-mediated effects or through paracrine growth factors. (78)

Remarkably, a clinical cohort study found that BMI was inversely associated with advanced stage; such that compared with normal-weight patients, overweight (OR= 0.61; 95%CI: 0.48 - 0.79) and obese (OR= 0.65; 95%CI: 0.51 - 0.83) patients had a decreased RR of the advanced stage disease even when adjusting for other comorbidities. (79)

Occupational exposure

Renal cell carcinoma (RCC) has traditionally not been considered an occupational disease, however, many studies have been conducted to investigate whether some exposures or specific job employment are linked with an elevated risk of kidney neoplasms. (80, 81) Particularly, many performed studies have analyzed the risk of RCC with exposure to certain metals, different fibres, dust and metalworking fluids, as well as which occupations and in-study patient characteristics are associated with this increased risk. (82, 83) In a nationwide, prospective epidemiological study, the risk of RCC was significantly associated in men, with a BMI over 25 kg/ m^2, suffering from self-reported kidney disease and elevated hypertension.(81) After correcting for these significant factors, farmers and horticulturists, printers, nursery workers (gardening), painters, aircraft mechanics and shipbuilders had a significantly increased risk of RCC. (81, 84) Cumulative exposure and duration has been showed to have a significant linear increase in RCC risk. (83)

Overall, lead exposure was associated with an increased risk of RCC, such that study patients exposed to lead had an overall risk of 1.70 (95%CI: 1.21 - 2.38; p=0.002) compared with

patients with no lead exposure.(82) Also, although not significant, in another study, those exposed to cadmium were at increased risk of RCC by 1.40 (95%CI: 0.69 - 2.85) with the highest overall risk to lead exposure of 2.25 (95%CI: 1.21 - 4.19).(80) Additional analysis in a case-control study was performed to those with exposure to more than one metal. Notably, the overall risk for the exposure to lead and cadmium was 2.77 (95%CI: 1.00 - 7.68). (80)

Further, exposure to different types of fibre dusts also increase the risk of RCC. Increased risk was observed among patients who were ever subjected or exposed to glass fibres (OR: 2.1; 95%CI: 1.1 - 3.9), mineral wool fibres (OR: 2.5; 95%CI: 1.2 - 5.1), and brick dust (OR: 1.5; 95%CI: 1.0 - 2.4). (83) Exposure to metal working fluids (mean exposure of 18.8p mg/m^3-year) also increased overall risk of RCC by 1.11 (95%CI: 1.04 - 1.19). (85)

However, sunlight exposure, even at its highest level, has been proven to reduce the risk of kidney cancer. In an occupational cohort study of Swedish construction workers, it was observed that men with the highest degree of exposure had a significant 30% decrease in kidney cancer (86). Another cohort study revealed that increased vitamin D production was associated with lower risk of kidney cancer (and other second primary cancers).

Race

Incidence rates for kidney cancer, renal cell carcinoma (RCC) in particular, has been consistently rising over time; however, a shift in racial predominance from whites to blacks is now being observed. (66) Notably, in several racial studies, the black population is more predisposed with higher incidence rates compared to other races/ethnicities.(87) A case-control study by Karami et al. estimated the relative risk (RR) for any first-degree renal cell cancer in Caucasians and African-Americans to be 3.96 (95%CI: 1.45 - 10.84) among blacks

and 1.98 (95%CI: 0.99 - 4.03) among whites. The reported results were non-significant given some limitation of the study such as the low response in the control group (54.4%) and the study power.(88)

Clear cell and papillary are two main histological subtypes of RCC present among white and black populations, with different incidence rates associated with each race. (66, 89) In a study analysis using data from 18 population-based registries of the Surveillance, Epidemiology, and End Results (SEER) Program (n=84,255), clear cell RCC was significantly higher for whites than blacks (50% vs. 31% respectively), while black patients were more likely to have papillary RCC (23% vs. 9% respectively) compared to white patients (90). Further, compared to white cases, blacks patients were approximately four times more likely (HR 4.15; 95%CI: 3.90-4.42) to have papillary RCC and twice as likely (HR: 2.00; 95%CI: 1.81 - 2.22) to have chromophobe RCC than clear cell RCC (90). Other races, such as Asian and Pacific Islanders, were less likely to have papillary (HR: 0.50; 95%CI: 0.43 - 0.59) and chromophobe (HR: 0.80; 95%CI: 0.67 - 0.94) than whites. (90)

Moreover, overall survival (OS) was longer for white patients than for black patients (p=0.0002); median survival for white and black patients was 11.5 and 6.9 months, respectively. The reason for this discrepancy in the outcome is still unknown. (91)

The relative risk for RCC differs according to race and gender, such that the age-adjusted incidence rates of renal cell cancer among black men, white men, black women, and white women were 20.0, 17.4, 9.6 and 8.8 per 100 000 person-years, respectively. (90) It is still unclear if specific genetic disposition would be the premise for the differentiation in race and gender.

Anemia

A common sign of renal cell carcinoma (RCC) is anemia, a condition marked by a deficiency of red blood cells or of hemoglobin in the blood. Anemia has been reported in 35% to 52% of patients with advanced RCC and is associated with more advanced disease and worse survival.(92) Anemic status can be determined by the level of hemoglobin (Hb) and haematocrit (Hct) detected at diagnosis.(93) In a 1994 to 2008 study comprised of 1307 patients with RCC who underwent a nephrectomy, patients with preoperative anaemia, assessed by Hb and Hct, had a 3.11-fold (95%CI: 1.17 - 8.25) and 6.20-fold (95%CI: 2.30 - 16.72) greater risk of mortality, respectively, compared with patients without anaemia.(93) More specifically, 5-year cancer specific survival (CSS) rates before surgery decreased amongst RCC anemic patients compared to those without anemia: 74.5% (95%CI: 68.4-79.5) and 93.9% (95%CI: 91.7 - 95.6) as measured for Hb and 78.7% (95%CI: 73.4 - 83.1) and 93.1% (95%CI: 90.7 - 94.9) for Hct (p<0.01).(93)

Many reasons could explain the role of anemia in having a worse cancer prognosis. In fact, it could presumably affect tumour hypoxia, a low quality of life, or poor responses to treatment. (93, 94) There is evidence that tumour hypoxia may play a negative role in cancer treatment and survival, either directly by the scarcity of oxygen that is observed to be resistant to radiation-induced DNA damage in tumours or indirectly through stimulating proteomic and genomic changes that subsequently lead to malignant progression.(92) Physical weakness, vulnerability to infection and undernutrition are common with anemia, and can contribute to poor general health and therefore poor prognosis. (93)

Given the biological role of the kidney in filtering blood and fluids, exposure to environmental toxins that are filtered by the kidney can have a direct impact on this organ and expose the kidney to oncogenic factors. In addition, the identification of many chromosome alterations has advanced our knowledge on the impact of these alterations on kidney cancer incidences.

1.5 Clinical manifestation

Clinical manifestation can play an important role in the diagnostic algorithm of RCC. Many observational studies have looked into the prevalence of specific clinical manifestation and their potential link to RCC diagnosis. This section depicts the known clinical manifestation commonly analyzed in the diagnosis of RCC.

Cachexia

Cachexia is a dramatic wasting syndrome, invariably associated with several chronic diseases including cancer, and is characterized by an involuntary weight loss, loss of muscle mass, anorexia, asthenia, anemia and alterations in carbohydrate, lipid and protein metabolism. (95, 96) Cancer cachexia occurs in the majority of cancer patients, affecting up to 80%, and results in weakness, reduced physical function, diminished quality of life, poor response to therapy,

and increased susceptibility to illness. (96) More specifically, in one study comprised of 667 patients with ccRCC with at least 1 present paraneoplastic syndromes of cachexia, 267 (40.0%) patients had a confirmed cachexia. (97) The degree of cachexia is inversely correlated with the survival time of the patient and it is usually related to a poor prognosis. Currently, there are no approved and effective treatments for muscle wasting in cancer. (95) However, the introduction of targeted anti-angiogenic therapy has dramatically enlarged the number of therapeutic options for the treatment of RCC and significantly improved the prospects for patients. (96, 98) Also, the competition for nutrients between the tumour and the host leads to a quicker catabolism state, which promotes hypermetabolism and could lead to an increased energetic inefficiency.(99-102) This syndrome (cachexia) is believed to be caused by the secretion of cytokines or hormones from the tumour or the immune system. (96, 103)

Erythrocytosis

Erythrocytosis is marked by an absolute increase in red blood cell mass and is also associated with an increased hematocrit (HCT) and hemoglobin concentration. Similarly, some use the term polycythemia interchangeably; however, these two are not synonymous. Polycythemia in precise terms refers to an increased number of any hematopoietic cell in blood, be it RBCs, platelets or leukocytes. (104) Erythrocytosis is rare, and occurs in 1 to 5 percent of patients with advanced RCC and appears to be due to constitutive production of erythropoietin.(105) Erythropoietin is a hormone found in mammals and produced mainly by the kidney.(106,

107) Higher Erythropoietin values are seen in patients with mixed RCC compared to those with the clear cell type. (108)

Secondary polycythemia (more specifically Erythrocytosis) is a heterogeneous group of disorders in which an elevated red cell mass occurs as a result of tissue oxygenation or the inappropriate production of erythropoietin or other erythropoietic factors.(109) Erythropoietin (EPO) production in liver and kidneys is inversely related to oxygen availability, which leads to negative feedback control of erythropoiesis. Studies of EPO regulation led to the identification of the transcription factor hypoxia-inducible factor (HIF, which is known to play a role in the upregulation of VEGF tyrosine kinase. (110)

Fever

Fever, an increase in body temperature above 37.5˚C, is recurrent and is often associated with night sweats, weight loss, fatigue and anorexia.(111, 112) In RCC patients, palpable renal mass, general malaise anorexia, weight loss, acceleration in erythrocyte sedimentation rate, liver dysfunctions and an increase in alpha 2-globulin were all significantly accompanied by fever.(113) The rate of occurrence of fever for patients with RCC varies per source; however, the vast majority of sources have concluded that fever occurs in up to 20% of patients.(112, 114) Limited information is available describing the biological mechanisms of RCC and fever. Naturally occurring fever is induced by a circulating endogenous pyrogen (EP). White blood cells stimulated by exogenous pyrogens (“activated” leucocytes) contain EP and will release this material in the presence of tumour factors. It appears, therefore, that the source

of EP in patients with RCC is either from the tumour cells themselves or from a mixed population of 'inactive' and 'activated' leucocytes within the tumour. (111)

Hepatic Dysfunction

Renal cell carcinoma (RCC) is uncommonly associated with paraneoplastic symptoms, in particular hepatic dysfunction. More specifically, hepatic dysfunction is described as Stauffer syndrome in the absence of liver metastases. Hepatic dysfunction in RCC is attributed to interleukin-6 (IL-6) and other cytokine production from the tumour.(115-117)

IL-6 plays a role in the growth of tumours as it induces the expression of receptors for hematopoietic growth factors on progenitor cells and accelerates their entry into the cell cycle; increase in serum IL-6 levels in 50 to 80% of patients with mRCC. IL-6 stimulates the proliferation and maturation of megakaryocyte progenitors and the proliferation of monocytes and polymorphonuclear neutrophil (PMN) progenitors.(115)

Another hepatic dysfunction related to RCC is the identification of paraneoplastic serum alkaline phosphatase elevation. Elevation of serum alkaline phosphatase has an estimated incidence of 21.1% (77 of 365) and represents another one of the manifestations of paraneoplastic syndromes in RCC patients. (118)

It has been observed that in some patients, paraneoplastic serum alkaline phosphatase elevation return to normal after resection of the tumours implying that the tumour itself may have elaborate alkaline phosphatases or substances that cause elevation of serum alkaline phosphatase. This is similar to Whitakerg and Stolbach *et al.* who also suggested that renal

cell carcinoma was the cause of serum alkaline phosphatase elevation and that removal of the tumour led to a dramatic decline of serum alkaline phosphatase level. (118)

Hypercalcemia

Hypercalcemia is a metabolic disorder in which there is an abnormally high calcium level present in the blood.(119) Hypercalcemia affects approximately 20 to 30% of cancer patients, and is associated with poor prognosis.(119) More specifically, hypercalcemia occurs in approximately 3 to 13% of patients with renal cell carcinoma.(120) A higher incidence rate of 16.8% (n=160) is present with advanced disease.(120) Approximately 90% of the patients with an increase of serum calcium have the primary hyperparathyroidism or hypercalcemia of malignancy as a cause.(119) Normal serum calcium levels range from 8.5 to 10.2 mg/dL.(119) In mild hypercalcemia, the serum calcium values are between 11 to 11.5 mg/dL.(119) Hypercalcemia in the mild stage remains asymptomatic and can only be detected through the routine measurement of calcium levels. (119) Calcium levels higher than 12 and 13 mg/dL can cause lethargy, stupor and gastrointestinal symptoms. Patients with serum calcium levels between 15 and 18 mg/dL are considered to have serious hypercalcemia, and it is considered a medical emergency due to the risk of cardiac arrest and coma. (119)

The most common cause of clinically significant hypercalcemia is malignant diseases. (121) Humoral hypercalcemia of malignancy (HHM) is a form of cancer-associated hypercalcemia due to the production and release of humoral factors by the malignant cells.(121) Further,

overproduction of parathyroid hormone-related protein (PTH-rP) is implicated in the hypercalcemia of malignancy, particularly in the case of solid tumours. (122) Notably, higher levels of serum PTH-rP have been associated with advanced disease, resistance to calcium lowering agents and shortened survival.(123) However, like PTH-rP, IL-6 has also been implicated in the syndrome of humoral hypercalcemia, and can enhance the action of PTH-rp and stimulate osteoclastic bone resorption.(122) Patients with metastatic RCC and hypercalcemia may benefit from nephrectomy resulting in a temporary decrease in serum calcium level following surgery, but not if hypercalcemia is due to diffused bone metastasis. (123)

1.6 Staging of RCC

1.6.1 TNM Staging

Until the 1990s, the most commonly used staging system for RCC was the Robson's modification of the system of Flocks and Kadesky. However, many limitations of the system such as the combination of lymphatic metastases with those with venous involvement were found. Further imprecision resulted from the fact that the extent of venous involvement was not delineated in this system, and tumour size, an important prognostic parameter, was not incorporated. This inappropriate classification resulted in reporting of similar outcomes in stage II and III tumours. (1, 47)

Table 1: Robson renal cell carcinoma staging system

Tumour stage	Description
Stage I	Confined to the kidney
Stage II	Involvement of the perinephric fat, limited to Gerota fascia
Stage III	
IIIa	Renal vein involvement
IIIb	Nodal involvement
IIIc	Both renal vein and nodal involvement
Stage IV	
IVa	Direct invasion of adjacent structures
IVb	Distant metastasis

Currently, the most utilized staging tool for RCC is the TNM system, which was developed by the International Union Against Cancer and the American Joint Committee on Cancer. The TNM staging, which was originally proposed in 1978, is in its seventh edition. In light of the increasing trend for the discovery of very small tumours as incidental findings on imaging studies performed for other purposes, revisions to this 1997 version have been

proposed, including subclassification of T1 into T1a < 2.5 cm; T1b, 2.5–4.0 cm; and T1c, 5.0–7.0 cm tumours.

The system takes into account the influence that local factors such as perinephric fat invasion, invasion of the inferior vena cava wall, as well as lymph node involvement and distant metastasis at presentation can have on prognosis.(124)

TNM stages

Stage I (T1, N0, M0): The tumour is 7 cm across or is confined within the renal capsule (T1). There is no spread to lymph nodes (N0) or distant organs (M0).

Stage II (T2, N0, M0): The tumour is larger than 7 cm but is confined within the renal capsule (T2). There is no spread to lymph nodes (N0) or distant organs (M0).

Stage III: Either of the following: (T3, N0, M0): The tumour is growing into a major vein (renal vein or the vena cava) or into perirenal fat, but it is not growing into the adrenal gland or beyond Gerota's fascia (T3). There is no spread to lymph nodes (N0) or distant organs (M0).

(T1 to T3, N1, M0): The main tumour can be any size and may be outside the kidney, but it has not spread beyond Gerota's fascia. The cancer has spread to regional lymph nodes (N1) but has not spread to distant lymph nodes or other organs (M0).

Stage IV: Either of the following:

(T4, any N, M0): The main tumour is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant lymph nodes or other organs (M0).

(T, Any N, M1): The main tumour can be any size and may have grown outside the kidney (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes and/or other organs (M1)

1.6.2 Integetrated prognostic tools for mRCC patients

Prognostic tools are valuable to estimate survival of patients in RCC. Many studies have underlined clinical features linked to the survival of mRCC patients, which have been incorporated in integrated prognostic tools such as the MSKCC and the IMDC criteria.

MSKCC criteria

One of the most widely used prognostication systems is the one by the Memorial Sloan-Kettering Cancer Center (MSKCC) group that integrates five prognostic factors. Motzer *et al.* assessed several clinical and laboratory factors in a cohort of advanced RCC patients in order to identify markers of longer survival, even if the prognosis of these patients was poor.(125) The MSKCC criteria were evaluated with a population treated with cytokine therapy, before the development of targeted treatment. Several factors were found to predict survival in mRCC patients.

The following factors are part of the MSKCC criteria:

- A Karnofsky performance status (KPS) of < 80%
- Serum lactic dehydrogenase (LDH) level >1.5 times the upper limit of normal
- Corrected serum calcium >10 mg/dL (2.5 mmol/L)
- Hemoglobin concentration less than the lower limit of normal

- Absence of nephrectomy (i.e. no disease-free interval)

Patients with none of these risk factors versus those with one or two versus those with three or more risk factors had significantly higher survival rates at one year (71 versus 42 and 12 percent, respectively). Figure 5 presents the survival curves of patients by performance group. (125)

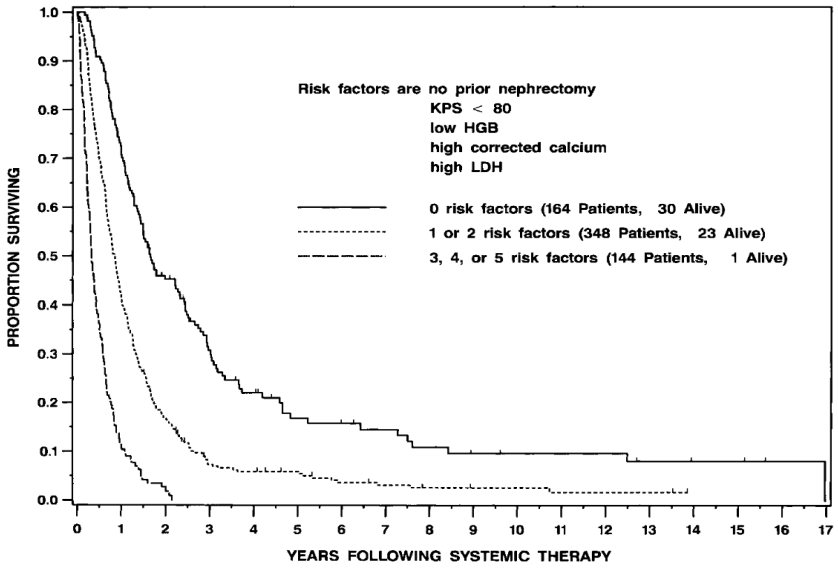


Figure 5:Survival stratified according to risk group (n=656).

Internal validity of the model was assessed with two-step non-parametric bootstrapping technique. The authors used 200 bootstrap samples and a stepwise procedure was applied to each sample using the same significance level for entering and removing a variable as in the original model. Risk ratio with a 95% confidence interval was estimated for each covariate in the final model.

Externally validity of the MSKCC criteria was completed with a follow-up study of 353 patients where the 5 initial criteria where confirmed and 2 additional criteria were found to be significant. In fact, prior radiotherapy and presence of hepatic, lung, and retroperitoneal

nodal metastases were found to be independent prognostic factors. According to Motzer's definitions, 19% of patients were favorable risk, 70% were intermediate risk, and 11% were poor risk; median overall survival times for these groups were 28.6, 14.6, and 4.5 months, respectively ($p<0.0001$). (126)

IMDC criteria

The International Metastatic renal cell carcinoma Database Consortium (IMDC) criteria were established for mRCC patients treated with targeted treatments in order to better assess the prognosis of these patients. Heng *et al.* developed this prognosis score based on clinical and laboratory features of mRCC patients.(127) Over 645 patients were analyzed for baseline characteristics from Canadian and US cancer centres. Many features were found to be independent predictors of short survival such as hemoglobin less than the lower limit of normal ($p<0.0001$), corrected calcium greater than the upper limit of normal (ULN; $p<0.0006$), Karnofsky performance status less than 80% ($p<0.0001$), and time from diagnosis to treatment of less than 1 year ($p<0.01$). In addition, neutrophils greater than the ULN ($p<0.0001$) and platelets greater than the ULN ($p<0.01$) were found to be independent prognostic factors for survival.

Patients were stratified in 3 groups depending on the number of prognosis factors they have as follows: the favorable-risk group, intermediate-risk group and poor-risk group.

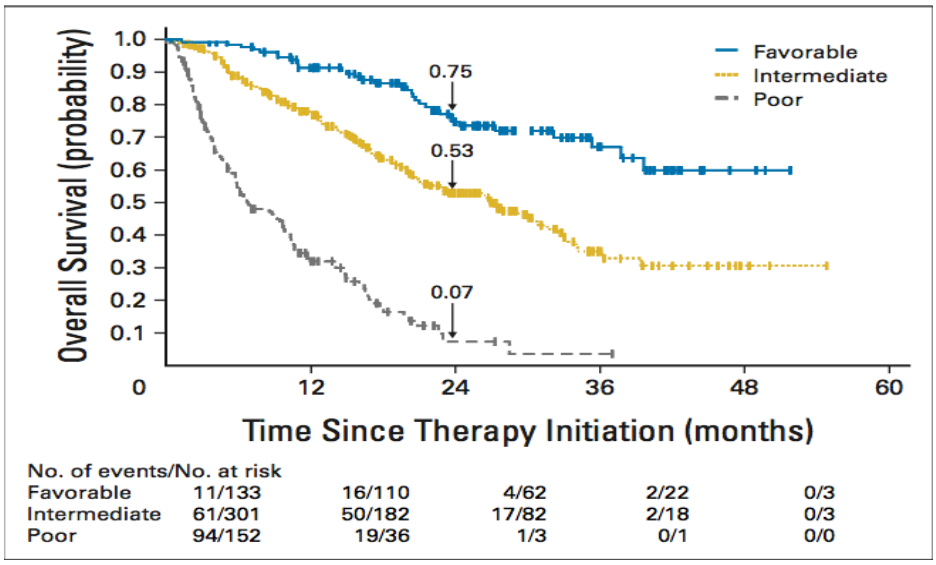


Figure 6:Survival curve of patients stratified by the IMDC criteria performance.

The favorable-risk group is defined as patients with none of the independent factors listed above. The 2 years OS is estimated to be 75% in this group of patients. The intermediate-risk group have 1 or 2 prognostic factors and a 53% 2-year OS. The poor-risk group has 3 to 6 factors and the 2 years OS is 7%. The 2 years OS difference between the 3 groups is statistically significant (p<0.0001). (Figure 6)

A study by Kwon *et al.* was completed in order to validate both the MSKCC and IMDC criteria in mRCC patients treated with VEGF therapy (sunitinib).The application of both criteria resulted in the stratification of the 135 patients included in the study in 3 risk groups (favorable, intermediate and poor) with statistically significant different OS curves. This study confirmed the validity of both criteria with high discriminatory abilities, (χ^2 = 30.82, Harrell's C = 0.6895) for the IMCD criteria and (χ^2 = 25.13, Harrell's C = 0.6532) in the MSKCC model.(128)

Prognostic tools in second-line therapy

The MSKCC criteria were also assessed in patients treated with second-line therapy. Survival in patients treated previously with mRCC was assessed in 251 patients treated in 29 clinical trials between 1975 and 2002.(129) Pretreatment features associated with a shorter survival in the multivariate analysis were high corrected serum calcium, low hemoglobin level, and low Karnofsky performance status. The median survival time in patients with zero risk factors, 1 risk factor and 2 to 3 risk factors was 22 months, 11.9 months and 5.4 months, respectively.(129)

The IMDC and MSKCC criteria were evaluated in patients previously treated with targeted treatment with the objective of assessing the applicability of the prognostic factors in this specific patient group.(130) The study included 1021 patients treated with second-line targeted therapy and the median OS was 12.5 months (95%CI: 11.3 - 14.3). Five of six predefined factors in the IMDC model (anemia, thrombocytosis, neutrophilia, Karnofsky Performance Status [KPS] <80, and <1 year from diagnosis to first-line targeted therapy) were independent predictors of poor overall survival on multivariable analysis. The concordance index when using all of the 6 prognostic factors from the IMDC criteria was 0.70 and 0.66 with the 3 MSKCC factors for second-line therapy. (131)

The current prognostic-tool specific to RCC are commonly used given their internal and external validity in clinical practice and in the investigation of newer therapies in order to classify response to treatment by different risk groups.

Chapter 2: Management of Renal Cell Carcinoma

This chapter will cover the multiple treatment options such as pharmacotherapy or surgical resection and their respective clinical outcomes. In addition, established and emerging management strategies for the localized and advanced disease will be discussed as well as guidelines recommendations.

2.1 Management of localized disease

The management of localized RCC has significantly evolved with the findings of many studies looking into the impact of the tumour and patient characteristics on the survival and rate of progression. In fact, it has been demonstrated that the size of a tumour is proportionally linked to the risk of having a malignant disease.(132, 133) In addition to the rate of malignancy, tumour size also correlates with biologic aggressiveness for clinical T1 renal masses, as reflected by high tumour grade, locally invasive phenotype, or adverse histologic subtype. Frank *et al.* found less aggressive and invasive phenotype or high tumour grade in tumours less than 4 cm.(134) With the evidence of many studies looking at the size of tumours and its implication in the disease, many guidelines refer to a 3 to 4 cm mass to describe a small tumour in order to recommend the most optimal way of managing the mass. The recurrence of disease has been studied in many trials and was deemed related to the initial stage of the disease at diagnosis, notwithstanding the management approach. (135, 136) In fact, patients with initial stages of the disease pT3a and pT3b had an increased risk of recurrence compared to patients with pT1 and pT2, and recurrences were diagnosed earlier

with a median of 12 vs. 36 months. Many guidelines recommend the use of active surveillance, surgical resection and ablation for the treatment of localized disease. (137, 138)

2.1.1 Surgical resection

The management of localized RCC has changed greatly since the 1970's. In fact, the first study to demonstrate the benefit of radical nephrectomy for the management of RCC was published in 1969.(139) Leibovich *et al.* analyzed the rate of recurrence in patients undergoing radical nephrectomy.(140) The study included 1,671 sporadic patients with clinically localized, unilateral clear cell RCC who underwent radical nephrectomy between 1970 and 2000. Metastases occurred in 479 patients at a median of 1.3 years (range, 0 – 25 years) after nephrectomy. The estimated metastases-free survival rates were 86.9% at 1 year, 77.8% at 3 years, 74.1% at 5 years, 70.8% at 7 years, and 67.1% at 10 years. Cox regression analysis was completed to identify variables that might predict progression to metastasis and found tumour stage, regional lymph node status, tumour size, nuclear grade, and histologic tumour necrosis to predict progression.

In general, most clinical studies in surgical resection of localized renal masses have compared the use of radical versus partial nephrectomy in their analysis. This being said, a meta-analysis has looked into this question and found partial nephrectomy to be associated with a risk reduction of 61% in severe chronic renal disease and reduction in the risk of all-cause mortality by 19%. This analysis included 31,729 patients with the majority (77%) of patients undergoing radical nephrectomy. However, the main difference in outcome was found in patients over the age of 80 years-old. When the single study exclusive to octageners was excluded, the significant difference between partial and complete nephrectomy was not

found.(141, 142) Most studies included in the meta-analysis had patients with different characteristics, which brings significant heterogeneity in the meta-analysis: I^2 (87%-49%). In addition, a more recent meta-analysis was published in 2017 for T1b and T2 renal tumours treated with radical nephrectomy or partial nephrectomy.(143) This meta-analysis included 11,204 patients with 77% of patients having a radical nephrectomy (RN). Patients undergoing partial nephrectomy (PN) were younger and had smaller masses in general by 0.65 cm (p<0.001). Lower estimated blood loss was found for RN (p<0.001) and a higher likelihood of postoperative complications for PN was observed (RR: 1.74; 95%CI: 1.34 - 2.2; p <0.001). Partial nephrectomy was associated with a better postoperative renal function, as shown by higher postoperative estimated glomerular filtration rate (eGFR; p <0.001), lower likelihood of postoperative onset of chronic kidney disease (RR: 0.36; p <0.001), and lower decline in eGFR (p<0.001). The PN group had a lower likelihood of tumour recurrence (OR: 0.6; p<0.001), cancer-specific mortality (OR 0.58; p =0.001), and all-cause mortality (OR: 0.67; p =0.005).

In parallel, many studies have underlined the fact that RN is linked to deterioration of the renal function and high rates of Chronic Kidney Disease (CKD). Huang *et al.* studied 662 patients undergoing radical nephrectomy and monitored their renal function. The authors found the incidence of grade 3 CKD (eGFR < 60 mL/min/1.73 m^2) was much more common after RN than PN, 65% versus 20%, respectively (p <0.001). In addition, more severe CKD (eGFR < 45 mL/ min/1.73 m^2) was also much more common after RN than PN, 36% versus 5%, respectively (p <0.001).(144) After surgery, the 3-year probability of freedom from new onset of GFR lower than 60 mL/min per 1.73 m^2 was 80% (95%CI: 73 - 85) after partial

nephrectomy and 35% (95%CI: 28 - 43; p <0.0001) after radical nephrectomy.(144) More recently, tumours over 4 cm were compared when treated with partial or radical nephrectomy on the basis of renal function.(145) Patients undergoing PN had a smaller risk of developing significant GFR change following surgery than did those undergoing RN (p <0.0001). The use of RN (p <0.0001), preoperative GFR < 60 ml/min (p <0.0001), tumour size ≥ 4 cm (p <0.0001), and older age at diagnosis (p <0.0001) were found to be independent predictors for developing significant postoperative GFR loss. Given the fact that the presence of CKD is known to be a risk factor for the cardiovascular disease, the relative risks of cardiovascular events were 1.4, 2.0, 2.8, and 3.4 for eGFR (mL/min/1.73 m^2) of 45 to 60, 30 to 45, 15 to 30, and less than 15, respectively. (146) All these factors taken into consideration led to the revision of many guidelines for surgical resection of small renal masses.

In addition to open surgery, the use of laparoscopic and robotic approaches is now accepted as a standard for the resection of small renal tumours as it provides equivalent oncologic outcomes to open counterpart and with the advantage of more rapid recovery. It has been noted that patients chosen to undergo laparoscopic surgery have smaller tumour sizes (p <0.001) compared to open surgery and mostly under 4 cm.(147) In addition to tumour size, patients undergoing partial nephrectomy have a decreased performance status and impaired renal function, as noted by Gill *et al.*(148) It has been shown that ischemia time is much longer with laparoscopic surgery (p <0.0001), but the hospital stay and blood losses are much less with this intervention by 3 days and 173 ml, on average, respectively.(147, 148) Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open

partial nephrectomy appears to be similar. In fact, cancer-specific survival at 3 years was not significantly different between laparoscopic and open surgery with less than 1 % in difference.(148, 149)

Guidelines recommend the use of nephrectomy, whether partial or radical depending on patient characteristics; both associated with different benefits and risks, between long-term renal function and expected cancer-free survival. As a matter of fact, many factors are taken in consideration when selecting the appropriate surgical resection such as the size of the tumour, the location of the tumour and the presence of multiple or bilateral tumours, and the presence of solitary kidney or compromised renal function.(Table 2)

Table 2: Guidelines for surgical resection using nephrectomy for localized disease

NCCN(138)	ESMO(150)	EAU(151)	CUA(152)	AUA(137)
Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example: Unilateral Stage I-III tumours where technically feasible. Or uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer	Partial nephrectomy (PN) is recommended as the preferred option in organ-confined tumours measuring up to 7 cm (elective indication). PN can be carried out via open, laparoscopic or laparoscopic robot-assisted approaches. Laparoscopic RN is recommended if PN is not technically feasible. In patients with compromised renal function, solitary kidney or bilateral tumours, PN is also the standard of care, with no tumour size limitation (imperative indication). In tumours over 7 cm Laparoscopic RN is the preferred option.	PN is recommended in patients with T1a tumours. PN should be favoured over RN in patients with T1b tumour, whenever feasible. Laparoscopic RN is recommended for patients with T2 tumours and localized masses not treatable by PN.	Open partial nephrectomy is preferable to laparoscopic nephrectomy, when feasible. Partial nephrectomy can result in complications including bleeding, a need for transfusion, urinary fistula and acute changes in renal function.	Prioritize PN for the management of the cT1a renal mass when intervention is indicated. 2. Prioritize nephron-sparing approaches for patients with an anatomic or functionally solitary kidney, bilateral tumours, known familial RCC, preexisting CKD, or proteinuria. 3. Consider nephron-sparing approaches for patients who are young, have multifocal masses, or comorbidities that are likely to impact renal function in the future. Physicians should consider RN for patients where increased oncologic potential is suggested by tumour size, RMB, and/or imaging characteristics. In this setting, RN is preferred if all of the following criteria are met: 1) high tumour complexity and PN would be challenging even in experienced hands; 2) no preexisting CKD/proteinuria; and 3) normal contralateral kidney and new baseline eGFR will likely be > 45ml/m^2.

2.1.2 Thermal ablation

Other treatment methods have been developed to decrease the burden of surgical resection such as thermal ablation through the percutaneous or laparoscopic approach. There are two main thermal ablations that have been studied in RCC patients, which are cryoablation and radiofrequency ablation. The following section describes the use of both options in RCC patients and their respective outcomes.

Cryoablation (CA)

Cryoablation consists of rapid freezing of the tumour cells followed by gradual thawing, and repetition of the freeze-thaw cycle.(153) Several studies have compared cryoablation to nephrectomy or partial nephrectomy in order to compare the efficacy and morbidity between both interventions. A systematic review was conducted and included 6,875 RCC lesions in total. This meta-analysis demonstrated that difference in patient's characteristics was consistent across many studies, proving the presence of a tailored approach to manage surgical resection.(154) As such, differences in age, tumour size and median follow-up were found to be significantly different between CA patients and PN patients. In addition, local progression has consistently been higher with CA compared to PN (p<0.001), but CA is related to fewer comorbidities (p<0.001). Some characteristics such as tumour size and the number of probes used during the procedure were found be predictors of complications with odd ratios of 2.85 and 1.94, respectively.(155) Progression to metastatic disease is not significantly different between both modalities. Caputo *et al.* evaluated the efficacy of CA compared to PN for cT1b renal masses.(156) During the study period, a total of 31 patients

were treated using CA and 161 using PN. After matching, there was no significant difference between the PN and CA groups and there was no significant difference in percentage eGFR preservation between PN and CA (89% vs 93%; $p = 0.5$). The rate of local recurrence was significantly higher for CA than for PN ($p = 0.019$). There was no significant difference in cancer-specific mortality ($p = 0.5$) or overall mortality ($p = 0.15$) between the CA and PN groups. In the same lane, Guillotreau *et al.* investigated the role of CA compared to PN and found similar demographic difference between both groups.(157) For example, patients undergoing CA were much older ($p<0.0001$) and tumour size was significantly bigger in patients undergoing PN ($p=0.004$). This study included 446 patients in total and included SRMs of 4 cm or less. PN was associated with longer operative time (180 vs 165 min; $p = 0.01$), increased estimated blood loss (200 vs 75 ml; $p < 0.0001$) and higher morbidity rate (20% vs 12%, $p = 0.015$). However, local recurrence rates for PN and CA were 0% and 11%, respectively ($p < 0.0001$). Limited information is found on long-term efficacy of CA, but some small retrospective studies have looked into the rates of recurrence and disease progression after CA.(158-160) The 10-year recurrence-free survival rate was 95% and the 10-year disease relapse-free survival rate was 81% for patients undergoing CA. When compared to PN, the median OS is similar between both groups at 3 and 5 years but cancer-specific and recurrence-free survival were superior in the PN group ($p<0.05$).(159) Finally, CA is an effective, alternative option to surgical resection as stated in many observational analyses, but patients and clinical characteristics are important criteria in the selection of CA as the most optimal option.

Radiofrequency ablation

Radiofrequency ablation is another form of thermal ablation using heat instead of cold. Mechanistically, heat above 45° C leads to irreversible cellular damage, and temperatures higher than 55° C to 60° C result in immediate cell death. Direct heat causes denaturation of intracellular protein and cellular membrane, which in its turn will cause tumour destruction.(161)

A meta-analysis compared the efficacy of cryoablation and radiofrequency.(162) Forty-seven studies representing 1,375 kidney lesions treated by CA or RFA were analyzed in a meta-analysis. No differences were detected between ablation modalities with regard to mean patient age (p=0.17), tumour size (p=0.12), or duration of follow-up (p=0.53). Pretreatment biopsy was performed more often for cryoablated lesions (82.3%) than for RFA (62.2%; $p<$ 0.0001). Unknown pathology occurred at a significantly higher rate for SRMs that underwent RFA (40.4%) versus CA (24.5%; p<0.0001). Repeat ablation was performed more often after RFA (8.5% vs 1.3%; $p<$ 0.0001), and the rates of local tumour progression were significantly higher for RFA (12.9% vs 5.2%; p<0.0001) compared with cryoablation. The higher incidence of local tumour progression was found to correlate significantly with treatment by RFA on univariate analysis (p<0.001) and on multivariate regression analysis (p<0.003). Metastasis was reported less frequently for CA(1.0%) versus RFA (2.5%; $p<$ 0.06). (162)

Many studies have looked into the outcomes of RFA compared to surgical resection. OS, DSS and renal function have all been assessed in different observational studies. However, a strong selection bias is found in these studies given the difference in patient's characteristics between TA and surgery. In fact, many studies show a significant difference in the median age between the RFA group and the surgery groups, with an average difference of 10 years.

Choueiri *et al.* investigated the Surveillance, Epidemiology and End Results (SEER) database from 2004 until 2007 to identify T1-N0M0 RCC patients undergoing thermal ablation (whether CA or RFA) or surgery. Out of 15,145 patients, 578 underwent TA, and the rest had a surgery. In multivariable adjusted analyses, single status (p= 0.02), male gender (p = 0.01), increasing age (p < 0.01), year of diagnosis (p < 0.01), and smaller tumour size (p < 0.01) were strong independent predictors of TA use compared with surgery (PN or RN). This being said, a significant difference in 10-year survival is seen between patients undergoing RFA compared to surgical ablation in many studies (HR: 1.9; p=0.02).(163, 164) However, disease-specific survival does not seem to differ between both modalities.(163, 165) Thompson *et al.* compared PN, RFA and CA in a retrospective cohort where 1,057 underwent PN, 180 underwent RFA, and 187 underwent cryoablation. In this cohort, local recurrence-free survival was similar among the three treatments (p= 0.49), whereas metastases-free survival was significantly better after PN (p= 0.005) and CA (p = 0.021) when compared with RFA. (166)

New modalities in radiotherapy are being assessed since many limitations are present with thermal ablation, whether RFA or CA. In fact, they are typically limited to small renal masses and lesions located away from the collecting system and vascular structures because of the risk of heat sink effects or fistula development.(167) With larger tumours, there is a significant risk of hemorrhage, which can require major intervention to control. To conclude, patients with advanced age and significant comorbidities that prefer a proactive approach but are not candidate for surgical resection might benefit the most from thermal ablation. In addition, patients with local recurrence after previous nephrectomy can benefit from this approach as well.

2.1.3 Active surveillance (AS)

While surgical therapy remains the cornerstone of treatment in localized disease, some patients may be poor surgical candidates to go under the knife, as surgical resection may not always be an ideal solution for elderly patients with significant comorbidities. In addition, many patients present with small renal masses who tend to be benign in over 20% of cases, which may not require treatment if asymptomatic.(168) The AUA guidelines for management of the clinical T1 renal mass recommend AS as the primary consideration for patients with decreased life expectancy or extensive comorbidities that would make them high risk for intervention.(169) In September 2017, the AUA released their newest guideline for renal mass and localized renal cancer and provided detailed recommendation on the management of patients with AS. Table 3 depicts the recommendation from different guidelines on AS.(137)

Table 3: Guidelines recommendation for active surveillance in localized disease.

NCCN (138)	Active surveillance is an option for the management of localized renal masses and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive intervention. Short- and intermediate-term oncologic outcomes indicate that an appropriate strategy is to initially monitor small renal masses, and, if required, to treat for progression.
ESMO (150)	Active surveillance is an option in elderly patients with significant co-morbidities or those with a short-life expectancy and solid renal tumours measuring <40 mm. The growth of renal tumours (mean 3 mm/year) is low in most cases, and progression to metastatic disease is reported in 1%–2%. Renal biopsy is recommended to select patients with small masses for active surveillance [III] with high accuracy.
EAU(151)	In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, RFA and cryoablation can be offered.
CUA(152)	Active surveillance with regular radiographic follow-up should be a primary consideration for SRMs in elderly and/ or infirm patients with multiple comorbidities that would make them high risk for intervention, and in those with limited life expectancy
AUA(137)	For patients with small, solid or Bosniak 3/4 complex cystic renal masses, especially those <2 cm, AS is an option for initial management. (Conditional Recommendation; Evidence Level: Grade C) For patients with a solid or Bosniak 3/4 complex cystic renal mass, physicians should

	prioritize active surveillance/expectant management when the anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment. (Clinical Principle) For patients with a solid or Bosniak 3/4 complex cystic renal mass in whom the risk/ benefit analysis for treatment is equivocal and who prefer AS, physicians should repeat imaging in 3-6 months to assess for interval growth and may consider RMB for additional risk stratification. (Expert Opinion) For patients with a solid or Bosniak 3/4 complex cystic renal mass in whom the anticipated oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend active treatment. In this setting, AS with potential for delayed intervention may be pursued only if the patient understands and is willing to accept the associated oncologic risk. (Moderate Recommendation; Evidence Level: Grade C)

Several observational studies have looked into the benefits of AS on patients by delaying the time to intervention. Bosniak *et al.* reported one of the first series on active surveillance (AS) that included 72 small (<3.5 cm) renal tumours in 68 patients who were observed with serial imaging studies for intervals ranging from 2 to 10 years (mean: 3.3 years) and found a delay in interventions for 70% of patients.(170) A retrospective analysis by Abou Youssif *et al.* looked into the outcomes of AS including 35 patients with a median age of 71.8 years between 1992 and May 2006.(171) This analysis found that age, comorbidity, solitary kidney or bilateral renal masses were all factors for choosing AS. The median tumour size at diagnosis was 2.2 cm and the mean dimension growth rate was 0.21cm/ year. Of the 35 patients, 2 (5.7%) were lost to follow-up, 8 (22.9%) underwent surgical resection, and 9 (25.7%) died of other causes. In the same lane, Abouassaly *et al.* reviewed retrospectively 110 patients from their institution who had been diagnosed with renal masses from 2000 to 2006.(172) The median age of the patients was 81 years (range 76 to 95) and the median tumour size was 2.5 cm. The Charlson comorbidity index was assessed and the median index was 2, putting most patients at risk with intervention. The median tumour growth rate was

0.26 cm/year. The authors did not find a statistically significant difference in the survival of patients whom disease was stable and patients with tumour growth (p=0.83). Similar retrospective studies have aligned conclusions on the role of AS in selected patients and the benefit of delaying active treatment by managing patients with AS.(172-175)

Chawla *et al.* underwent a review of the literature to identify studies that looked into untreated observed renal masses from 1966 to 2004.(176) They identified 286 patients and included 234 in their meta-analysis and included 7 publications.(170, 177-183) Many reasons were noted for the selection of AS in these patients such as delay in referral (22%), patient refusal to undergo surgery (53%) and extensive patient comorbidity (25%). The mean growth rate of the masses was 0.28 cm annually and the mean follow-up was 34 months. There was no association found between the lesion size at presentation and the overall growth rate (p=0.46). Only 1% of lesions progressed to metastatic disease.(176)

Similarly, Gupta *et al.* conducted a systematic review of the literature for studies looking into AS in small renal masses.(184) Fourteen clinical series (1,245 patients; 1,364 lesions) were included in the analysis. Mean lesion size at presentation was 2.30 ± 0.40 cm with a mean follow-up of 33.6 ± 16.9 months. Out of the 14 included studies, 34% of patients underwent delayed intervention and the average time of AS prior to definitive treatment was 27.8 ± 10.6 months. In 41% of cases, the decision was taken after tumour growth; and in 51.9% of cases, it was based on patient or physician preference in the absence of clinical progression. Overall, 1.1% of all patients progressed to metastatic disease during the mean follow-up. The mean growth rate of tumours that eventually underwent intervention was 0.70 ± 0.61 cm per year. In comparison, tumours that remain on AS demonstrated a mean growth rate of 0.28 ± 0.20 cm per year.

Jewett *et al.* analyzed a cohort of 178 patients prospectively under AS from 2004 until 2009 in order to evaluate their progression and survival outcomes.(185) Of the 178 subjects with 209 small renal masses (SRMs), 127 with 151 SRMs had > 12 months of follow-up with two or more images, with a mean follow-up of 28 months. Their tumour diameters increased by an average of 0.13 cm/yr. Needle core biopsy in 101 SRMs demonstrated that the presence of RCC did not significantly change growth rate. Likewise, Pierorazio *et al.* recently published the results from the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) where 497 patients with SRMs underwent AS versus primary intervention (PI).(186) Over a median follow-up of 2.1 years, 9% of patients on AS underwent delayed intervention. They found that AS was not inferior to PI for a well-selected cohort of patients: OS for PI and AS was 98% and 96% at 2 years, and 92% and 75% at 5 years, respectively (log rank, $p = 0.06$). Using the same registry (DISSRM), Patel et al. assessed the quality of life of patients on AS or PI.(187) Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least 1 year following the intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on active surveillance.

Finally, the evidence presented above from retrospective and prospective databases underline the outcomes of AS and the patient characteristics leading to the management of RCC with AS. In fact, most studies reported a median age over 70 years, which is higher than the median age of diagnosis of 62 years old in RCC patients and reports renal masses of < 4 cm at the time of diagnoses. In fact, Lane *et al.* demonstrated that active treatment in patients aged 75 years and older might not confer a measurable survival benefit over AS.(188) In addition,

most patients had significant comorbidities making surgery a high risk. The conclusions of these series from several institutions remain similar as the growth rate of these masses is relatively slow (median growth rate 0.28 cm/year), the median follow-up time is about 2-3 years, and a small number of patients will progress to metastatic disease (around 1%). Table 4 summarizes the main studies looking into AS in RCC patients.

Table 4: Summary of studies in Actives surveillance in SRMs.

Study	N	Mean age (years)	Mean initial tumur dimension (cm)	Mean linear growth rate (cm/year)	Mean surveillance follow-up (months)	Delayed intervention (%)
Bosniak (170)	40	66	1.73	0.36	39	70.3
Volpe(189)	32	71	2.93	0.10	28	27.6
Wehle(190)	29	70	1.83	0.12	32	31.0
Kouba(174)	46	67	2.92	0.70	36	30.2
Youssif(171)	44	72	2.20	0.24	48	22.9
Abouassaly(172)	110	81	2.50	0.26	24	3.6
Crispen (191)	172	69	2.50	0.29	31	44.2
Jewett(192)	209	73	2.10	0.26	28	12.9
Patel(187)	93	72	2.20	0.21	34	19.7
Pierorazio(186)	240	71	1.90	0.11	25	9.4

2.2 Advanced/metastatic renal cell carcinoma

The treatment landscape of advanced/metastatic RCC has greatly evolved with the introduction of oral pharmacotherapy to minimize tumour burden. In addition, research has demonstrated the impact of resection in late stages of the disease on PFS and disease burden. In some patients, active surveillance is deemed as an acceptable option for the management of the disease and to postpone the use of targeted therapies. All these available options in the management of the disease bring a lot of questions on the optimal sequence to treat patients. This section presents the different options to manage mRCC patients and their respective outcomes.

2.2.1 Metastasectomy

Surgery plays an important role in the management of mRCC patients in several ways. This surgical procedure can be conducted in different situations such as in patients who develop metastases following a nephrectomy or in patients who have persistent disease despite systemic therapy. Although metastasectomy has been successfully performed in various organs, favorable features that are more amenable to resection include solitary lesion (preferably in the lung), curative resection at first metastasis, metachronous presentation, disease-free interval greater than 12 months, and younger age at presentation. (193, 194) Several studies underlined the benefit of metastasectomy in mRCC patients in yielding long-term disease-free survival, which will be explained in the following section.

Guidelines

Many guidelines have issued recommendations for the management of advanced renal cell carcinoma and the surgical resection of tumours. Table 5 summarizes the guidelines' recommendation from 5 national and international societies. In general, the guidelines recommend assessing case-by-case the need for metastasectomy, especially based on patient characteristics, location of metastasis and performance status of the patient. In addition, the number of metastases as well as the size factors are to be considered.

Table 5: Metastasectomy guidelines recommendation

CUA(195)	In selected patients with limited sites of metastasic disease and clinically stability, resection of the metastatic disease may be reasonable.
AUA (137)	No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on case-by-case basis; performance status, risk profiles, patients' preference and alternative techniques to achieve local control, must be considered.
ESMO(150)	Metastasectomy for easily accessible pulmonary metastases, solidary resectable intra-abdominal metastases, a long disease-free

	interval after nephrectomy or a partial response in metastases to immunotherapy or targeted therapy. *No systematic treatment is recommended after metastasectomy.
EAU(151)	No general recommendation can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control, must be considered. In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for symptom relief.
NCCN(138)	Patients who initially present with primary RCC and a solitary site of metastasis or 2- develop a solitary recurrence after a prolonged disease-free interval from nephrectomy. Sites of solitary metastases that are amenable to this approach include the lung, bone and brain.

Clinical Studies

Alt *et al.* studied the benefits of complete metastasectomy for multiple RCC metastases. They included 887 patients between 1976 and 2006 who were diagnosed with multiple metastases either at the time of or after nephrectomy.(196) A survival advantage from complete metastasectomy was observed among patients with multiple metastases, who had a 5-year cancer specific survival (CSS) rate of 32.5% with complete resection versus 12.4% without complete resection (p <0.001). Overall, patients who did not have any resection of metastases in this study had a 3-fold increased risk of death from RCC. The authors noted that patients who underwent complete surgical resection were more likely to present initially with clinically localized RCC (p <0.001).(196) Kwak *et al.* assessed the role of metastasectomy combined with adjuvant immunotherapy, which did not result in a significantly higher overall survival rate as compared with metastasectomy alone. In the immunotherapy group, median overall survival was 56.1 months (95%CI: 34.1 - 78.2), whereas the no immunotherapy group reached a median overall survival of 21.3 months (95%CI: 3.4 – 39.2), respectively.(197)

Furthermore, Naito *et al.* evaluated 556 patients with mRCC who had either complete or incomplete resection of their metastatic sites and showed a survival benefit of more than 70 months for patients who underwent complete resection versus incomplete (109.8 vs. 31.9 months; p < 0.001). (198) This is consistent with another study from Daliani *et al.* who reported a median survival time of 5.6 years after complete resection versus 1.4 years for incomplete resection.(199) A meta-analysis assessed the outcomes following complete surgical metastasectomy in mRCC patients. In this analysis, all studies majorly included clear cell subtype and patients had received systemic therapy.(200) A total of 2,267 patients were included in the analysis, from whom 958

patients underwent complete surgical metastasectomy and 1,309 incomplete surgical metastasectomy. The median OS ranged between 36.5 and 142 months for patients managed with complete surgical metastasectomy and 8.4 to 27 months in patients treated with incomplete surgical metastasectomy. The pooled adjusted Hazard-Ratio (aHR) was 2.37 (95%CI: 2.03 - 2.87, p<0.001). Figure 7 illustrates the forest plot of the meta-analysis, showing a significant advantage for complete metastasectomy.

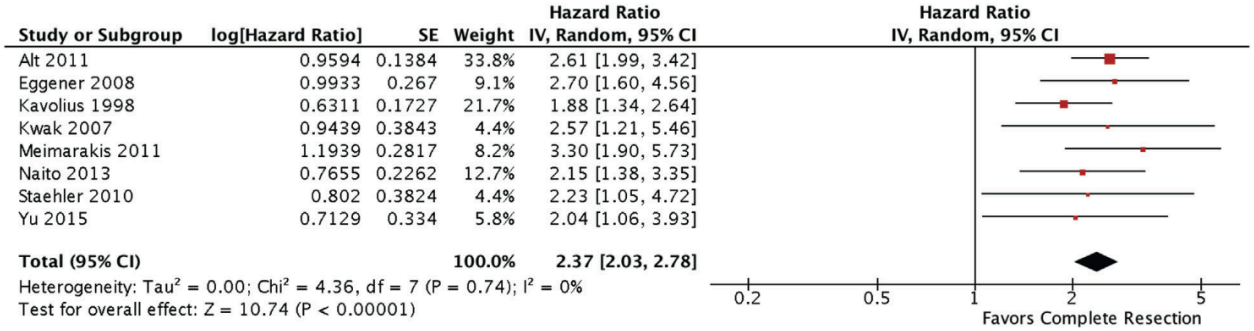


Figure 7:Forest-Plot of meta-analysis showing results of Overall mortality. Adapted from Zaid et al.(200)

Bone metastasis

Bone metastases are the second most common site of metastasis in mRCC patients with an incidence of 15-34%.(201) Fottner *et al.* studied the impact of metastasectomy on patients with bones metastases. They included 101 patients identified in hospital records between 1980 and 2005 from which 27 patients had a solitary bone metastasis, 20 patients had multiple bone metastases and 54 had concomitant visceral metastases. The OS was 58% at 1 year, 37% at 2 years and 12% at 5 years. The median OS was 15.8 months (IQ: 6.8 - 34.6 months) and patients with a solitary bone metastasis had a significantly better (p = 0.002) survival than patients with multiple bone metastases. (202)

In addition, Lin *et al.* assessed the survival of 295 mRCC patients with resection of osseous metastases.(203) The most common sites of bone metastases were the femur, humerus and pelvis.

OS at 1 and 5 years were 47% and 11%, respectively, with metastatic pattern having a significant effect on the survival rate.

Lung metastasis

The lung is the most common site of metastatic spread of mRCC with an incidence ranging from 45 to 75%. The resection of lung metastases had been studied back in 1939 suggesting the potential advantage in survival in selected patients.(204, 205) Alt *et al.* evaluated the benefit of resection of lung metastases in 887 mRCC patients. Complete metastasectomy was associated with a significant prolongation of median cancer-specific survival (CSS) (4.8 years vs 1.3 years; $p<0.001$).(196) Patients who had lung-only metastases had a 5-year CSS rate of 73.6% with complete resection versus 19% without complete resection ($p<0.001$). Moreover, on multivariate analysis, the absence of complete metastasectomy was associated significantly with an increased risk of death from RCC (HR: 2.91; 95%CI: 2.17 - 3.90) $p<0.001$.(196) In the same way, Kudelin *et al.* assessed the outcomes of pulmonary metastasectomy in mRCC patients. They included in their analysis 116 patients from January 1999 to December 2009, and 34.5 % of the patients were treated with systemic therapy before metastasectomy. The median OS was 56.6 ± 9.2 months and the OS rate at 5 years was 49%. A statistically significant difference was found in patients aged < 70 years old with a median OS of 67 months ($p<0.001$) (206). Assouad *et al.* evaluated the impact of the size of lung metastases on the survival after metastasectomy. Patients who had lung metastases smaller than 20 mm had a median OS of 54 months compared to patients with metastases greater than 20.01 mm who had a median OS of 22 months ($p=0.023$).(207)

An evaluation was conducted to identify prognostic factors after resection of pulmonary metastases in mRCC patients.(208) Two hundred and two consecutive patients entered the study and were treated with metastasectomy, complete or partial. The median overall survival after pulmonary

metastasectomy was 39.7 months (95%CI: 31.4 - 47.9 months), and the 5-year overall survival was 39%. Regression analysis reported complete metastasectomy (R0), metastasis size >3 cm, positive nodal status of the primary tumour, synchronous metastases, pleural infiltration, and tumour-infiltrated hilar or mediastinal lymph nodes as independent prognostic factors for survival.

Brain metastasis

The outcome for patients with RCC who develop brain metastases is typically poor, with median survival of only 4-11 months after diagnosis and 5-year survival of 12%.(209, 210) A study by Ikushima *et al.* compared brain metastasectomy followed by conventional radiotherapy (STRS) and conventional radiotherapy alone.(211) Median survival was 25 months for the STRS group, 18 months for the metastasectomy followed by conventional radiotherapy and 4 months for the conventional radiotherapy-only group. Significant prognostic factors associated with better survival were age less than 60 years and good performance status.

Liver metastasis

Liver metastasis occurs in about 20% of patients with mRCC with an OS of approximately 14 months.(205) The value of surgical resection of the liver has been studied in multiple observational studies in mRCC patients. Staehler *et al.* evaluated the survival of 88 patients undergoing resection of tumour liver and found the median OS to be 142 months (95%CI: 115 - 169) compared to 27 (95%CI: 16 – 38) months in the control group ($p = 0.003$). (212) The authors concluded that liver metastasectomy is an independent valuable tool in the treatment of metastatic RCC and significantly prolongs patient's survival, even if further systemic treatment is necessary. Stief *et al.* evaluated the outcome and survival of patients undergoing surgery for metachronous solitary liver metastases between 1983 and 1993 where 17 patients with metachronous liver metastases of renal cell carcinoma underwent laparotomy for metastatic liver disease. All patients had undergone

radical nephrectomy at a mean 3.6 years before the diagnosis of liver metastases. The median OS of unresected patients was 4 months compared to 16 months in patients who had a metastasectomy.(213)

To conclude, the summarized studies demonstrate significant advantages to the surgical removal of metastases. However, many studies looking into the outcomes of metastasectomy have significant bias selection since physicians tend to select patients with better prognostic factors. This being said, some studies did compare the survival when adjusting for these independent factors and found that surgical resection is still a valuable option in this setting.

2.2.2 Cytoreductive Nephrectomy

The role of cytoreductive nephrectomy (CN) in patients who have advanced or metastatic disease has been reviewed in many RCT and observational trials summarized below. The impetus for exploring this approach in mRCC was provided by the perception that bulky tumours might inhibit key components of the immune system critical for combatting cancer cells. Just like with metastasectomy, selection bias can be found in these trials as the exposure to surgery is usually linked to certain patient criteria. Two main phase 3 trials have looked at the efficacy of cytoreductive nephrectomy in mRCC patients in the era of cytokines.

The SWOG trial is a phase 3 study that included 241 patients with mRCC comparing interferon-α alone vs. interferon-α with surgery.(214) Patients were randomly assigned to each arm of the study and were followed for a median of 12 months. The primary endpoint was survival, and the secondary endpoint was the response of the tumour to treatment. There were no significant differences in the response rates to interferon-α observed in the two study arms; however, OS was improved in the surgery plus interferon arm (median 11.1 vs. 8.1 months for interferon alone, p = 0.05). The difference between both groups was independent of performance status, metastatic site,

and the presence or absence of a measurable metastatic lesion. In addition, the EORTC trials used a similar design and presented similar results with a total of 85 patients randomized to interferon-α alone or interferon-α after nephrectomy. This study reported a survival advantage favoring the CN plus interferon-α arm (median OS 17 vs. 7 months, $p = 0.03$).(215) A combined analysis of both trials revealed results that were consistent with those reported in the individual trials.(216)

More recently, observational studies have looked into the effect of CN in the era of targeted therapy and found a benefit to the inclusion of CN in the management of mRCC patients. A clear selection bias can be identified in most of these studies as mRCC patients who tend to go for a CN are younger and have a better prognostic score (IMDC or KPS). Choueiri *et al.* analyzed patients who underwent CN (n=201) who were younger ($p < 0.01$) and more likely to have a better KPS ($p < 0.01$), with more than 1 site of metastasis ($p < 0.04$) and with lower corrected calcium levels ($p < 0.01$) compared to those who did not undergo cytoreductive nephrectomy.(217) On univariable analysis, CN was associated with a median overall survival of 19.8 months compared to 9.4 months for patients who did not undergo CN (HR: 0.44; 95%CI: 0.32 - 0.59; $p < 0.01$). On multivariable analysis and adjusting for established prognostic risk factors, the OS difference persisted (adjusted HR: 0.68; 95%CI: 0.46 - 0.99; $p < 0.04$) in favor of the CN group.

More recently, Heng *et al.* conducted a retrospective analysis using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) in patients undergoing CN with advanced disease(218). Patient undergoing CN had better prognostic factors and less metastases. The difference in OS found was similar to Choueiri *et al.* with approximately 10 months of survival benefit. When adjusting for potential confounding variables, the HR was 0.60 (95%CI: 0.52 – 0.69; $p < 0.0001$).

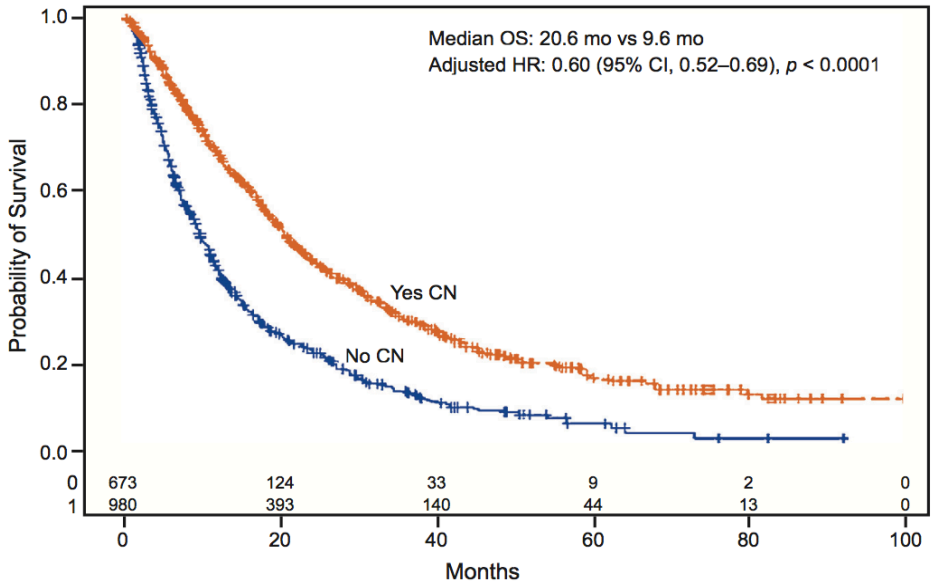


Figure 8: Overall survival of patients with or without CN. Adapted from Heng et al. (218)

In addition, a relationship between the estimated survival and incremental OS benefit was demonstrated. Incremental benefit analysis demonstrated that the only patient groups not to receive an OS benefit from CN were those estimated to survive < 3 months (2.2 vs 2.1 mo OS: +0.1; p=0.943). Patients estimated to survive < 6 months experienced a marginal +0.8 OS increase when a CN was performed (4.0 vs 3.2 months OS; p = 0.008). The longer a patient was estimated to survive, the greater the OS benefit of CN. The study showed that the subgroup of patients with an estimated OS <12 months and four to six adverse prognostic factors may not benefit from CN. A third retrospective study conducted by Mathieu *et al.* with the same objective to compare No CN vs. CN, and OS was significantly better with CN (16.4 vs. 38.1 months, p < 0.001), but only in patients who had a good ECOG (0 or 1 or a good to intermediate MSKCC score). On the contrary, this benefit was not significant for the patients with an ECOG score of 2 to 3 (8.0 vs. 12.6 months, p = 0.8) or the group with poor MSKCC score (5.2 vs. 5.2, p = 0.9). (219)

Beyond its efficacy, the use of CN has been documented in many studies between the 2 eras of cytokines and targeted therapies. Tsao *et al.* classified patients from the SEER database between both groups and looked at the patterns between patients undergoing CN or not.(220) Overall, 1,112 of 2,448 patients (45 %) underwent CN. Logistic regression analysis revealed that older age (OR: 0.82; 95%CI: 0.68 - 0.99), black race (OR: 0.64; 95%CI: 0.46 - 0.91), Hispanic ethnicity (OR: 0.71; 95%CI: 0.54 - 0.93), and treatment in the VEGFR-TKI era (OR: 0.82; 95%CI: 0.68 - 0.99) were independently associated with decreased use of CN.(220) The use of CN remained stable between 2001 and 2005 (50 %), but decreased to 38 % in 2008.

The SEER database was again used by Xiao *et al.* to look at factors related to the use of CN and its effectiveness in patients with mRCC. Age, race, tumour size, T stage and N stage were associated with CN. After matching based on propensity scores, the 1-, 2-, and 3-year cancer-specific survival rate estimates were 45.1%, 27.9%, and 21.7% for the no-surgery group vs 70.6%, 52.2%, and 41.7% for the CN group, respectively (HR: 0.42; 95%CI: 0.35 - 0.52, log-rank p<0.001). (221)

An additional populational study from Zini *et al.* looked at the mortality of mRCC patients comparing the ones who had a CN vs. no surgery. After matching for potential confounding variables, such as age and tumour size, the HR for mortality was 2.6, p< 0.001 for the no-surgery group.(222) In the same lane, the SEER database was looked at by Aizer *et al.* and found similar conclusions on the benefits of CN in mRCC patients when adjusting for many confounding variables.(223)

Capitanio *et al.* looked into the difference in survival between partial and radical nephrectomy in mRCC patients. They included 2,043 patients in the analysis and matched 1 PN to 4 RN. The tumour size was significantly different between both groups (9.3 vs. 5.1 cm, p<0.001). In the

unmatched analysis and matched analysis, the RCC specific-survival rates were different between both groups favoring PN in the unmatched (HR: 1.8; p=0.014) and matched (HR: 1.78; p=0.01) analysis, respectively. The authors concluded that there is no difference between partial and radical nephrectomy in the cancer-specific survival in mRCC patients.(224)

Many studies ought to investigate potential factors that can predict outcomes of CN in mRCC patients. Culp *et al.* published 2 studies from large population-based cohort identifying factors associated with RCC-specific survival in patients diagnosed with mRCC and undergoing CN. Age at diagnosis ≥ 60 years, African American race, higher American Joint Committee on Cancer T stage (≥ T_3), high Fuhrman nuclear grade (3 or 4), primary tumour size ≥ 7 cm, regional lymphadenopathy, both distant lymph node and visceral metastases, and sarcomatoid histology were all identified as factors independently associated with an increased risk of RCC-specific death. The second publication by Culp *et al.* looked into 566 mRCC patients from 1991 to 2007 who were eligible for targeted treatment. They identified many factors as independent preoperative predictors of inferior OS in surgical patients including a lactate dehydrogenase level greater than the upper limit of normal, an albumin level less than the lower limit of normal, symptoms at presentation caused by a metastatic site, liver metastasis, retroperitoneal adenopathy, supradiaphragmatic adenopathy, and clinical tumour classification ≥ T3. (225, 226)

2.2.3 Pharmacotherapy

Immunotherapy and targeted therapy are the primary systemic modalities for the management of patients whose disease is advanced and has metastasized. An understanding of the pathogenesis of RCC at the molecular level has identified the VEGF and mTOR pathways as important targets for therapeutic intervention. Further, the discovery of the PD-1/L1 target contributed to the

advancement in RCC. The following section describes the mechanism of action, efficacy and safety of targeted therapy in mRCC.

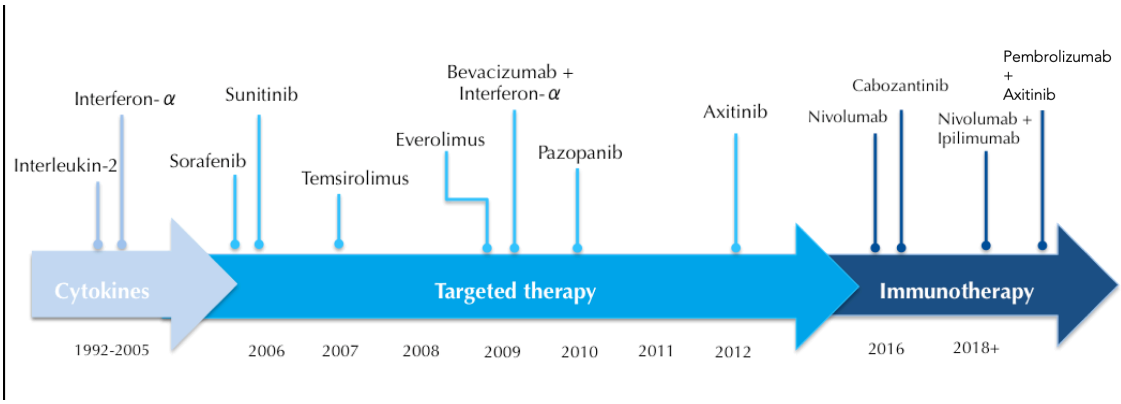


Figure 9: Molecules approved for mRCC in Canada by year.

Interferon- α

Interferon-α is a group of proteins with immunomodulatory properties and was one of the first cytokines to be evaluated for the treatment of mRCC. The initial response rates in phase 1-2 trials were between 10 % to 15%. The median overall survival for patients treated with interferon- α was about 8.5 months in randomized trials. In addition, interferon-α combined with vinblastine was found to yield higher response rates (16% vs. 2.5%) and improved OS (median 16 vs. 9 months, p=0.0049) compared to vinblastine alone.(227)

Interleukin-2

In 1992, the Food and Drug Administration approved the use of high-dose interleukin-2 for the treatment of RCC on the basis of phase 2 data, showing prolonged complete remission in approximately 7% of treated patients.(228) Interleukin-2 demonstrated an acceptable rate of complete regression (7%-9%) with the majority of these patients (60%) demonstrating no evidence of disease recurrence.(229) The objective response rate with interleukin-2 is estimated to be around

30%. The combination of both cytokines (interferon-α and interleukin-2) was assessed in a randomized trial and was deemed more effective, but no difference was observed in the OS of patient who compared to interferon- α or interleukin-2 alone.(230)

Bevacizumab

Bevacizumab is the only monoclonal antibody used in mRCC patients. This antibody binds to the VEGF and prevents its interaction with the VEGF receptor in order to decrease tumour growth and angiogenesis.(231)

The efficacy of bevacizumab was assessed in combination with interferon-α in untreated patients in 2 randomized-trials comparing it to interferon-α plus placebo. Both trials showed an improvement in PFS (10.2 versus 5.5 months, HR: 0.63; 95%CI: 0.45 - 0.72) in the AVOREN trials and 8.5 versus 5.2 months, HR: 0.71; 95%CI: 0.61 - 0.83) in the CALGB 90206 trial.(232, 233) However, the difference in OS was not statistically significant in both studies. Given the design of both randomized studies, the efficacy of bevacizumab solely has not been assessed. The combination of bevacizumab with interferon-α is not practical compared to oral VEGF inhibitors such as sunitinib as the administration has to be done in hospital setting because of the bevacizumab administration. Consequently, the utilization of this combination is less practiced in the management of mRCC patients.

More recently, bevacizumab was introduced in the evaluation of newer targeted therapy such as atezolizumab in the IMmotion 150 study in previously untreated mRCC patients compared to sunitinib.(234)

VEGF inhibitors

The role of VEGF receptor in RCC was discovered by studies attempting to identify the genetic basis of the von Hippel-Lindau familial kidney cancer syndrome. It was observed that individuals

carrying germline VHL mutations are at an increased risk for developing tumours in multiple organs, including clear cell kidney cancer.(235) VHL, a classic tumour suppressor gene, is inactivated in up to 80% of sporadic cases of clear-cell carcinoma by deletion, mutation, or methylation.(23, 236, 237) This tumour-suppressor gene encodes a protein that is involved in the regulation of the making of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and numerous other hypoxia-inducible proteins. Inactivation of the *VHL* gene causes overexpression of these agonists of VEGFR and PDGFR, and the resulting persistent stimulation of the receptors may promote tumour angiogenesis, tumour growth, and metastasis. (23, 235, 238-240)

One of the better-understood functions of the VHL protein is its association with elongins B and C and CUL2 to form a protein complex that serves to tag certain cellular proteins for degradation by the ubiquitin system.(22, 239, 241-243) Proteins targeted for ubiquitin-mediated degradation include the α subunits of a group of transcriptionally active proteins known as hypoxia-inducible factors (HIFs).(238, 244-246) Mutations in VHL interfere with its binding to HIF or elongin/CUL2, which promotes the accumulation of HIF. The accumulation of HIF leads to the upregulation of a proangiogenic and growth factors, including VEGF and PDGF. This upregulation transforms many proteins such as growth factor-α, Glut-1 and erythropoietin, which are all believed to play a critical role in the development and progression of clear cell RCC.(238, 243) Figure 9 illustrates the molecular cascade involved in the inhibition of VEGFR and PDGFR.

This molecular discovery led to the development of many molecules targeting the VEGF receptor in order to block this upregulation by inhibiting the receptor. Molecules targeting the VEGF receptors and approved in Canada for clear cell mRCC are sunitinib, pazopanib, axitinib, sorafenib,

and more recently, cabozantinib. The following pages will depict the efficacy of these targeted treatments in clear cell mRCC patients.

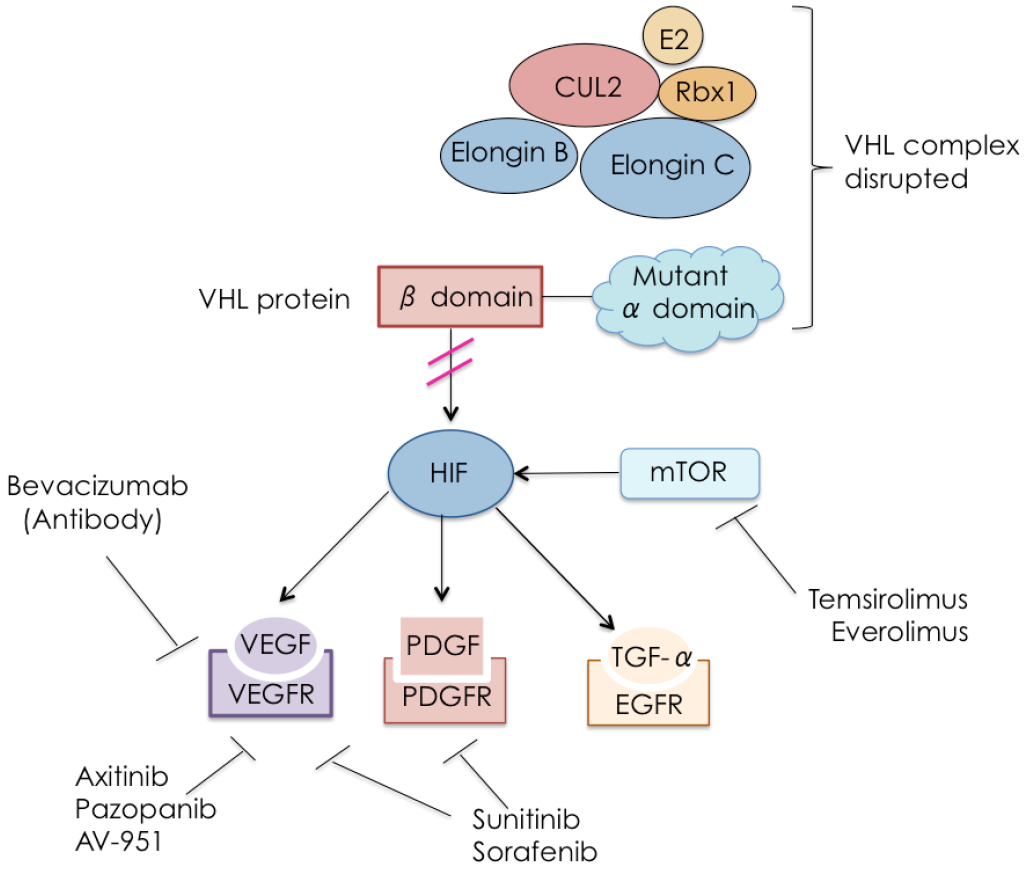


Figure 10:VHL pathway and its targeting through targeted therapies. Adapted from Campbell-Walsh Urology.(1)

Sunitinib

Sunitinib is an oral tyrosine kinase inhibitor targeting the VEGF and PDGF receptor. This interaction is supposed to lead to the inhibition of the proliferation and angiogenesis of the tumour, which leads to the shrinkage of the tumour.(247) In Canada, Sunitinib is officially indicated as a first-line treatment for clear-cell mRCC and gastrointestinal stromal tumour (GST) after failure of imatinib mesylate treatment due to resistance or intolerance.(248)

Efficacy

The first phase 3 RCT assessing the efficacy of sunitinib in mRCC patient was published in 2007 by Motzer *et al.*(249) This study compared sunitinib to interferon-α (IFN-α) in 750 patients who were not previously treated with any systemic treatment. The interim analysis demonstrated a statistically significant difference in the PFS (11 vs. 5 months HR: 0.42). Median overall survival was 26 months with sunitinib vs. 22 months for IFNα regardless of stratification (*P*-value ranges from 0.051 to 0.0132, depending on statistical analysis).(250)

Head-to-head trials against other targeted therapies were conducted, mainly comparing sunitinib and pazopanib. Motzer *et al.* assessed the non-inferiority of pazopanib vs. sunitinib in a RCT demonstrating a non-significant difference in the OS between both therapies.(251) Many observational studies around the world assessed the efficacy of sunitinib in first-line mRCC patients; however, the median OS tend to vary between studies from 17.3 to 31.7 months.(252-254) Many factors can be attributed to this difference between studies such as the dosing schedules and the performance status of the patients.

Schedule

The recommended dosage of sunitinib is 50 mg daily for 4 weeks, followed by 2 weeks off for a total of 6 weeks. Every 6 weeks is considered a cycle of treatment, but dose modification of 12.5 mg is recommended based on individual safety and tolerability(248). Contemporary studies with sunitinib have demonstrated the efficacy and safety of different regimens using hospital databases. The main purpose of attenuating the dose of sunitinib is to decrease the incidence of side effects affecting treatment continuation.(255)

Many factors seem to be associated with increased toxicities when treated with sunitinib, such as age, sex (female) and body surface. Intriguingly, those three factors could be potentially related to

increased sunitinib exposure when the drug is administered as a fixed dose without any adjustment.(256) The pharmacokinetic and pharmacodynamics of sunitinib have been assessed to understand the relation between the plasma concentration of sunitinib and the appearance of toxicities. When comparing the standard sunitinib schedule (4 weeks on; 2 weeks off) vs. schedule 2/1 (2 weeks on; 1 week off), both treatments have the same dose intensity in a 6-week period, and both of them have a rest period that permits patients to recover from toxicities. However, during a 4/2 schedule, patients start to experience sunitinib-induced toxicities at the second week of treatment, and the severity regularly increases over the next 2 weeks.(257) This means that the probability to observe an adverse event in the 4/2 schedule is higher in comparison with the alternative schedule 2/1. In the latter case, sunitinib administration is halted at day 14, before adverse events could worsen, and 1 week off treatment is likely enough to allow the complete recovery from mild, low-grade adverse effects.(258) Figure 10 represents the probability of side effects depending on plasma concentration. This pharmacokinetic explanation is supported by many studies and 1 meta-analysis studying the relationship between toxicities and reduced time off therapy.(255)

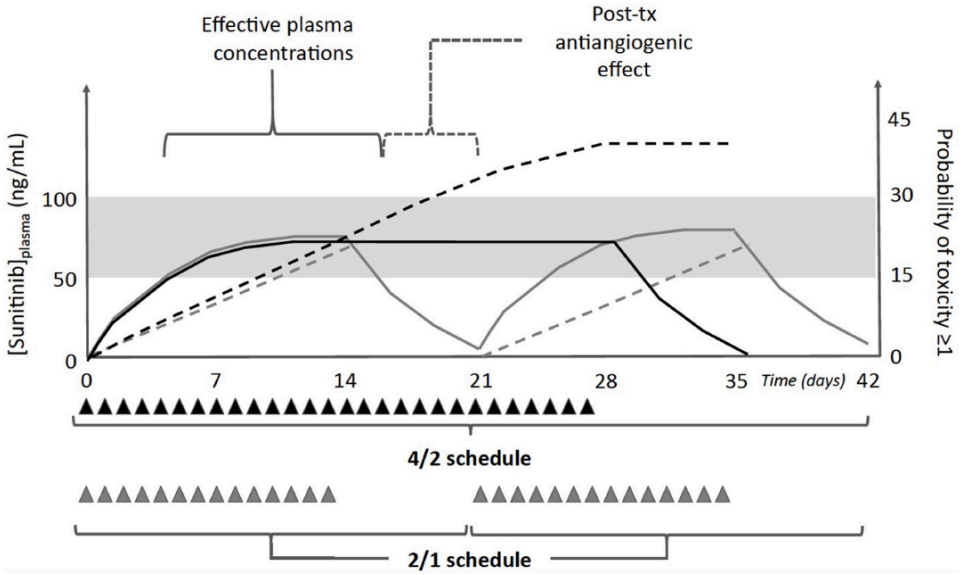


Figure 11:Probability of toxicity based on plasma concentration of sunitinib. Adapted from Houk et al.. (255)

Najjar *et al.* reviewed retrospectively 30 patients from the Cleveland clinic who were treated with sunitinib for mRCC. Patients were initiated on a 4/2 schedule and then switched to schedule 2/1.(257) There were statistically less toxicities in schedule 2/1 with no grade 4 AEs and only 27% of patients experiencing grade 3 toxicities compared to 97% of patients in schedule 4/2 experiencing AEs (p=0.0001). Atkinson *et al.* included 187 patients in their analysis looking into 2/1 schedule of patients who were initiated on 4/2 and changed after first intolerable AE.(259) There was a control group managed with 4/2 in order to compare the incidence of AEs and OS. The incidence of fatigue decreased by 54% when switching to schedule 2/1 and 73% for hand and foot syndrome. Median overall survival was 17.7 months (95%CI: 10.8 - 22.2) on the traditional schedule compared to 33.0 months (95%CI: 29.3 - not estimable) on alternative schedules (p <0.0001). The RAINBOW study by Bracarda *et al.,* a retrospective, multicenter analysis of mRCC patients treated with first-line sunitinib on a 2/1 schedule included 249 patients.(260) The authors found significantly less fatigue and hand and foot syndrome in the schedule 2/1group (p <0.001). However, there was no difference in the OS or PFS.

Kondo *et al.* evaluated 48 patients treated with schedule 4/2 or 2/1. The incidence of most adverse events was not significantly different between the two groups except for hand–foot syndrome and diarrhea, which were observed more frequently in schedule 4/2 and reached statistical significance. A dose interruption due to adverse events in the first three cycles was significantly lower in schedule 2/1 patients than in those on schedule 4/2 (27% versus 53% p <0.04) and median progression-free survival was longer in patients on schedule 2/1 than those on schedule 4/2 (18.4

versus 9.1 months), but this difference was not statistically significant (p=0.13). Table 5 lists several studies presenting the incidence of adverse events between both schedules.

Table 6: Incidence of side effect by study

	Fatigue			**Hand & foot syndrome**		
	Traditional	Alternative	RRR	Traditional	Alternative	RRR
Atkinson(259)	64%	29%	54.6%	38%	10%	47.4%
Najjar (257)	70%	53%	24.3%	50%	17%	66%
Pan (261)	86%	65%	24.4%	84%	61%	27.4%
Miyake(262)	51%	29%	49%	55%	33%	40%
Kondo (263)	86%	73%	15.1%	86%	58%	32.6%
Bracarda(264)	74%	67%	9.4%	55%	41%	25.5%

The quality of life of patients on schedule 2/1 has been reviewed in 2 studies. FKSI-19 and SF-36 were used as instruments to report the quality of life of patients on schedule 4/2 and 2/1. (261, 262) Both studies concluded that the quality of life of patients on schedule 2/1 is enhanced compared to schedule 4/2.

Another dosage that has been assessed for sunitinib is an attenuated dosage of 37.5 mg continuous daily dose instead of 50 mg with similar schedule 4/2; however, it did not demonstrate any advantage compared to the standard dose. Motzer *et al.* looked into the 37.5 mg continuous daily dose vs. the standard 4/2 schedule in a phase 2 RCT.(265) No significant difference was observed in overall survival (23.1 *v* 23.5 months; p= 0.615), commonly reported adverse events or patient-reported kidney cancer symptoms. Schedule 4/2 was statistically superior in time to deterioration, a composite endpoint of death, progression, and disease-related symptoms (p = 0.034).

Another study looked into the attenuated dose of 37.5 mg on a 4/2 schedule vs. 50 mg. There was a statistically significant difference in the OS and PFS (OS: 27.4 vs. 21.8 months, respectively;

p<0.45; PFS: 6.7 vs. 7.9 months, respectively; p<0.64), However, there was a statistically significant difference in the rate of AEs, with more AEs in the 50 mg group (p=0.0005).(266)

Several studies have underlined the association between toxicities and efficacy of sunitinib. For instance, hypertension was found to be a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.(267) Patients with mRCC and sunitinib-induced hypertension had better outcomes than those without treatment-induced hypertension (objective response rate: 54.8% vs 8.7%; median PFS: 12.5 months, 95%CI: 10.9 to 13.7 vs 2.5 months, 95%CI: 2.3 to 3.8 months; and OS: 30.9 months, 95%CI : 27.9 to 33.7 vs 7.2 months, 95%CI: 5.6 to 10.7 months; $p < 0.001$ for all). Donskov *et al.* assessed the relationship between toxicities and clinical outcomes. On-treatment neutropenia and hypertension were associated with longer PFS (p=0.0276 and p<0.0001, respectively) and OS (p = 0.0014 and p<0.0001, respectively), independently of baseline prognostic factors, including IMDC criteria. By 12-week landmark analysis, neutropenia was significantly associated with longer PFS and OS (p = 0.013 and p = 0.0122, respectively) and hypertension or hand–foot syndrome with longer OS (p= 0.0036 and p =0.0218, respectively).(268)

Pazopanib

Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptors (VEGFR)-1/-2/-3, platelet-derived growth factor receptors (PDGFR)-a/-b and stem cell factor receptor c-Kit.(269) In Canada, pazopanib is indicated for the treatment of mRCC naïve patients.(270)

Pazopanib was initially compared to placebo as second or first-line treatment. In fact, Hutson *et al.* demonstrated that pazopanib significantly improved PFS versus placebo in the overall study population (median PFS, 9.2 versus 4.2 months; HR: 0.46; $p < 0.0001$) and in the treatment-naive

(median, 11.1 versus 2.8 months; HR: 0.40; p<0.0001) and cytokine-pretreated subgroups (median, 7.4 versus 4.2 months; HR: 0.54; p<0.001).(271) The updated results of this randomized trial demonstrated the efficacy of pazopanib in PFS but not OS due to early and frequent crossover. In the treatment-naïve population, median PFS was 11.1 versus 2.8 months (HR: 0.40; p<0.0001). An updated survival analysis showed no statistically significant difference in OS (22.9 versus 20.5 months, HR: 0.91).(272)

In order to assess the efficacy of pazopanib compared to sunitinib, a randomized trial was conducted.(251) Motzer *et al.* demonstrated similar median OS between pazopanib and sunitinib (HR: 1.05; 95CI: 0.9 - 1.22). However, patients treated with sunitinib, as compared with those treated with pazopanib, had a higher incidence of fatigue (63% vs. 55%), hand–foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), but patients treated with pazopanib had a higher incidence of increased levels of alanine aminotransferase (60%, vs. 43% with sunitinib). (251) In parallel, the PISCES study was conducted to examine the quality of life of patients on sunitinib or pazopanib treatment. Given the lower rate of adverse events, more patients preferred pazopanib (70%) over sunitinib (22%), but 8% expressed no preference (p <0.001).(273)

Outside of randomized studies, pazopanib has been reviewed in many institution and countries. Valderrama *et al.* analyzed 278 patients treated with pazopanib in first-line setting in Italy. The median OS found was 22 months and the PFS, 11 months. In addition, the authors assessed the IMDC score of all patients and found the majority of patients having an intermediate performance score (57.2%), while 19.4% had a favorable score and 23.4% had a poor risk score.(274) This repartition is similar to many other publications looking at the performance status of mRCC patients undergoing targeted treatment.(130, 254, 275, 276)

DaCosta *et al.* reviewed patients retrospectively on pazopanib and sunitinib and matched patients through a propensity scoring. After matching, the duration of treatment for both drugs was similar: (p=0.445) 62.8 days vs. 55.6 days in the pazopanib and sunitinib group, respectively. (277) Vogelzang *et al.* compared 522 patients in each arm on the basis of their OS and reported an incremental difference of 3.6 months when patients were treated with sunitinib (18.2 vs. 14.6 p=0.015).(278) In the same lane, Santoni *et al.* compared 269 patients treated with sunitinib, pazopanib and sorafenib and found a significant difference in PFS, with an incremental 5.9 months with sunitinib compared to pazopanib and sorafenib (20 vs. 14.1 vs. 14.1 months; $p < 0.001$).(279) Finally, pazopanib has been evaluated in many studies and demonstrated to increase survival in mRCC patients as first-line therapy. In observational studies, we observe that in patients with poorer performance status, pazopanib is seemed to be preferred compared to sunitinib given the lower risk of adverse events.

Axitinib

Axitinib is another VEGF inhibitor recommended for second-line treatment. It has been investigated by Motzer *et al.* who reported an increase PFS in patients treated with axitinib vs. sorafenib in second-line setting; 8.3 months (95%CI: 6.7 – 9.2) with axitinib and 5.7 months (4.7–6.5) with sorafenib (HR: 0.65, 95%CI: 0.55 – 0.78; p<0.0001). However, the OS was not statistically different between both groups.(280) This trial showed a high objective response rate, and significantly prolonged progression-free survival of axitinib when compared with sorafenib. Consequently, it is the first drug that has supported the notion of sequencing tyrosine kinase inhibitors in second-line treatment in phase 3 randomized trials.

Both treatments were then studied in phase 3 randomized trials for first-line mRCC. However, this trial did not show an incremental benefit to axitinib, but on the contrary, it yielded a numerical

advantage in PFS with sorafenib (10.1 months (95%CI: 7.2 – 12.1) vs. 6.5 months (95%CI: 4.7 – 8.3), respectively; stratified HR 0.77 (95%CI: 0.56 – 1.05).(281) The difference between both trials is thought to be linked to the performance status of patients being different between both studies and the dosage adjustment.

Given the utilization of everolimus in second-line, axitinib was compared to everolimus in several observational studies. Vogelzang *et al.* retrospectively assessed the survival of patients on everolimus (n=325) and axitinib (n=157) using medical records. After adjusting for patient characteristics, there were no statistically significant differences in OS or PFS between everolimus and axitinib; HR: 1.02 (95%CI :0.67-1.55) and PFS HR: 1.07 (95%CI: 0.70 - 1.64). When stratifying by type and duration of first tyrosine kinase inhibitor (TKI), there was no statistically significant difference in OS between everolimus and axitinib in all subgroups except for patients with <6 months on sunitinib or sorafenib as first TKI HR: 1.09; (95%CI: 0.09 - 2.09). (282, 283)

A Japanese observational study analyzed 58 patients treated with axitinib in second-line therapy in order to identify prognostic variables. The median PFS for the axitinib treatment was 10.9 months (95%CI: 5.8 - 13.5), and the median OS from the start of axitinib treatment was 39.8 months (95%CI: 25.9 - NR). The authors found several side effects to be prognostic variables. In fact, on-treatment hypertension, hand-foot syndrome and hypothyroidism were associated with longer PFS (p= 0.0002, 0.0055 and 0.0290, respectively). (284)

Sorafenib

Sorafenib is a VEGF inhibitor but also targets other receptors such as C-raf and both mutant and wild-type B-raf. This additional inhibition is thought to play a role in tumour shrinkage given that the B-raf pathway is activated in over 50 % of RCC cases.(285)

Sorafenib has been studied both in first and second-line treatment where its use has been deemed to be limited to second-line patients. In fact, sorafenib (n=97) was compared to interferon-α (n=92) in previously untreated patients in phase 2 trials. The median PFS was equivalent between both treatment arms (5.7 vs. 5.6 months) in the sorafenib and interferon- α group, respectively. Nonetheless, the quality of life of patients was assessed in parallel and was found to be superior in the sorafenib arm given the appearance of fewer side effects.(286)

In second-line setting, sorafenib was again compared to interferon- α in a phase 3 study (TARGET) where 903 patients were randomized. The median PFS was significantly longer in patients receiving sorafenib compared with placebo (5.5 vs. 2.8 months, HR: 0.44; 95%CI: 0.35 - 0.55). Given that crossover was permitted in this study, no statistical difference was observed between both arms, as patients were crossing over to the sorafenib group.(287)

As mentioned in the axitinib section, randomized trials evaluated the difference between axitinib and sorafenib in the second-line setting. Axitinib was associated with higher adverse event rates but improved the PFS of patients compared to sorafenib.(281, 288)

Cabozantinib

Cabozantinib is a small oral molecule targeting many receptors such as c-Met, VEGFR2, AXL and RET. MET is a proto-oncogene that encodes a cell surface receptor for ligand hepatocyte growth factor. Mutations in MET that result in constitutive activation of the tyrosine kinase domain lead to increased unregulated proliferation, invasion and metastases. (289)

The main phase 3 study compared cabozantinib to everolimus in second-line and yielded a significant improvement in PFS and OS in patients treated with cabozantinib. Median progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus, HR (0.58; 95%CI: 0.45 - 0.75; p<0.001). (290)

The objective response rate was 21% with cabozantinib and 5% with everolimus (p<0.001). Adverse events were managed with dose reductions since 60% of patients treated with cabozantinib had an adverse events and 25% of those who received everolimus. The median OS was reported in a second unplanned analysis where the estimated OS for cabozantinib and everolimus were 21.4 months (95%CI: 18.7 – not estimable) with cabozantinib and 16.5 months (14.7 – 18·8) with everolimus (HR: 0.66; 95%CI: 0.53 - 0.83; p=0.00026). (291)

A network meta-analysis was done to compare the OS of nivolumab and cabozantinib in second-line. This network meta-analysis demonstrated an advantage for cabozantinib in the first 5 months, but was inverted to favor nivolumab afterwards. The initial probability of cabozantinib conferring superior OS was 54%, falling to 41.5% by month 24.(292) At the moment, cabozantinib is under investigation in previously untreated mRCC patients compared to sunitinib in the CABOSUN trial.(293)

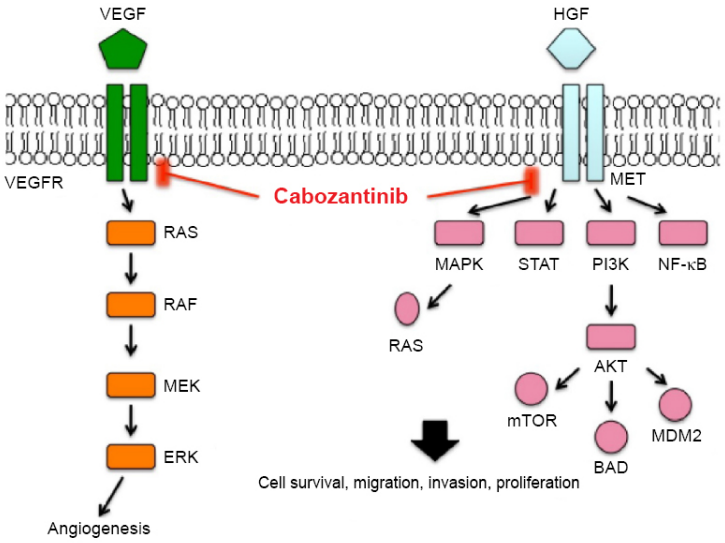


Figure 12: Cabozantinib mechanism of action. Adapted from Yu et al.(294)

Lenvatinib

Levantinib is a third-generation VEGF, orally administered, multiple receptor tyrosine kinase (RTK) inhibitor. It has a novel-binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other pro-angiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFR α; KIT; and RET) involved in tumour proliferation.(295)

Lenvatinib was the first VEGF inhibitor to show significant improvement in PFS in second-line treatment when compared to everolimus. Median progression-free survival was 12.8 months (95%CI: 7.4–17.5) in the lenvatinib plus everolimus group, 9.0 months (5.6–10.2) in the lenvatinib group, and 5.6 months (3.6–9.3) in the everolimus group. Progression-free survival was significantly longer in patients in the lenvatinib plus everolimus group than in those in the everolimus group HR: 0.45 (95%CI: 0.27 – 0.79; p=0.0029). (296)

mTOR inhibitors

The Mammalian Target of Rapamycin (mTOR) is a key protein that is a component of several cascades, which includes some cascades related to growth factors, metabolism, proliferation and motility. mTOR is a serine–threonine kinase, a member of the phosphatidyl inositol 3′ kinase family. More specifically, this protein is thought to play a role in the regulation of translation and stability of HIF-1α. The inhibition of mTOR is another target and key intracellular protein in the management of RCC tumours. This molecular pathway is targeted by many drugs such as temsirolimus and everolimus.(297)

Temsirolimus

Temsirolimus is the only targeted therapy that has been evaluated in patients with poor performance status. Temsirolimus binds to an abundant intracellular protein, FKBP-12, and in this way forms a complex that inhibits mTOR signaling. By inhibiting this signaling, the production of protein that regulates the progression and angiogenesis of tumours becomes disrupted. The inhibition of angiogenesis in RCC is known to downregulate tumour growth.(298, 299)

Hudes *et al.* published the first randomized phase 3 trial involving temsirolimus, comparing it to interferon-α in poor prognosis patients who were untreated. Patients who received temsirolimus alone had longer overall survival (HR for death: 0.73; 95%CI: 0.58 to 0.92; p=0.008) and progression-free survival (p<0.001) than did patients who received interferon alone. The side effect profile of temsirolimus was deemed better as fewer grade 3 or 4 side effects were found (p=0.02).(300)

In second-line, temsirolimus was compared to sorafenib in 512 patients previously treated with sunitinib. No difference was found in the PFS between both groups (4.3 vs. 3.9). However, the median OS in the temsirolimus and sorafenib arm was 12.3 and 16.6 months, respectively (p=0.01). The observed difference in median survival is suggested to be linked to treatment with the sequenced VEGF inhibitors, i.e., sunitinib, followed by sorafenib.

A retrospective study compared temsirolimus to everolimus in patients previously treated with sunitinib (n=89). Median PFS at second line was 4.3 months (95%CI: 3.7 - 4.8) in patients treated with everolimus and 3.5 months (95%CI, 3.8 - 4.5) in those treated with temsirolimus (p = 0.63). The OS was 35.8 and 38.3 months (p = 0.73) with sunitinib followed by everolimus and sunitinib followed by temsirolimus, respectively. (301)

The difference between everolimus and temsirolimus has been analyzed in a meta-analysis, including 4 observational studies and 937 patients from January 2006 until May 2014. Treatment with everolimus decreased the risk of death by 26% over temsirolimus (HR: 0.74; 95%CI: 0.59 - 0.93; $p < 0.008$), and reduced the risk of treatment failure by 30% (HR: 0.70; 95%CI: 0.56 - 0.88; $p= 0.002$). (302)

Everolimus

Everolimus is another mTOR inhibitor, mostly used in second-line setting after a VEGF inhibitor. Similarly to temsirolimus, everolimus targets the mTOR receptor, specifically the mTORC1 that leads to hyper-activation of the kinase AKT. Ultimately, this hyperactivation will reduce cell growth and proliferation.(303)

Everolimus was assessed in a phase 3 study (RECORD-1) comparing to placebo as second-line treatment. Patients were randomized 2:1 in the everolimus (n=277) to placebo (n=139). The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (HR: 0.33; $p < 0.001$). Serious adverse events with everolimus, independent of causality, in <5% of patients included infections (all types, 10%), dyspnea (7%), and fatigue (5%). The median OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR: 0.87; $p <0.162$), with 80% of patients in the placebo arm crossed over to everolimus. (304) This was the pivotal study to confirm the efficacy of everolimus and to include it in many kidney cancer guidelines as an option in second-line setting. The Record-1 trial was then used to assess the impact of various prognostic factors on overall survival and found the baseline sum of longest tumour diameters (SLD) and appearance of a new lesion or

progression of a nontarget lesion at first assessment after baseline also affects OS in patients with mRCC treated with everolimus.(305)

Several observational studies have looked into the effectiveness of everolimus compared to other second-line treatments using hospital databases. These analyses showed similar survival compared to randomized trials. In fact, the median PFS of everolimus was found to be ranging from 4.6 months to 6.9 months. (306, 307)

In the same way as temsirolimus, the side effect profile of mTOR inhibitor is particular to infection and lung diseases. Joly *et al.* evaluated 274 patients in a prospective observational study in France, finding many patients to have grade 3 stomatitis (8%) and lung diseases (3%).(308)

Given the high utilization of everolimus in second-line, it has recently been compared to the newest generation of VEGF inhibitor, cabozantinib, in previously treated mRCC patients. (309) Also, everolimus was compared in a phase 2 study in combination with lenvatinib for second-line treatment.(296) Phase 3 trials are ongoing to determine the efficacy of this combination. Finally, everolimus is continuously being studied in second-line with novel therapies, which suggests that it might still have a space in the management of mRCC.

PD-L1/PD1

The latest molecular development in oncology has identified the PD1 and PD-L1 as a target for the upregulation of tumours. PD-1 inhibitors and PD-L1 inhibitors are a novel group of checkpoint inhibitors developed for the treatment of several cancer types such as melanoma, lung and kidney. PD-1 and PD-L1 inhibitors act to inhibit the association of the programmed death-ligand 1 (PD-L1) with its receptor, programmed cell death protein 1 (PD-1).(310) The concept of blocking PD-1 and PD-L1 for the treatment of cancer was first published in 2001.(311) Biotechnology

companies began to develop drugs to block these molecules, and the first clinical trial was initiated in 2006, evaluating nivolumab.

Nivolumab

Nivolumab is a fully human immunoglobulin G4 programmed death-1 immune checkpoint used to treat many cancers such as lung, melanoma and kidney. The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. (312)

Nivolumab blocks the activity of a molecule called PD-1, a protein that prevents T cells from recognizing and attacking inflamed tissues and cancer cells. PD-1 can trick the immune system into overlooking malignant cells as normal cells. The strategy of immune checkpoint blockade is to reduce inhibitory signaling and restore the patient's natural tumour-specific T-cell-mediated immune responses.(310)

Malignant cell activates the PD-L1 inhibitors which bind to the T cells and prevent the T cells from killing the malignant tumour. Nivolumab blocks the PD-1 and PD-L1 interaction in order to allow T cell to kill the malignant tumour.(310)

Phase 3 study of nivolumab vs. everolimus (CheckMate 025) included 821 patients, and had as primary clinical endpoint the difference in OS, and as second endpoint the objective response rate and safety.(313) The median overall survival was 25.0 months (95%CI: 21.8 to not estimable) with nivolumab and 19.6 months (95%CI: 17.6-23.1) with everolimus. The HR for death with nivolumab vs. everolimus was 0.73 (98.5%CI: 0.57 - 0.93; p=0.002), which met the prespecified criterion for superiority ($p \leq 0.0148$). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; OR, 5.98 (95%CI: 3.68 -9.72); $p<0.001$). The median PFS was 4.6

months (95%CI: 3.7 - 5.4) with nivolumab and 4.4 months (95%CI, 3.7 - 5.5) with everolimus (HR: 0.88; 95%CI: 0.75 - 1.03; p=0.11). Fewer Grade 3 or 4 treatment-related adverse events occurred in the nivolumab group (19%) compared to the everolimus group (37%); the most common event with nivolumab was fatigue (in 2% of the patients), and anemia with everolimus (8%).(313)

Of the patients treated with nivolumab, 48% were treated beyond progression based on RECIST. A subset of patients with advanced renal cell carcinoma and disease progression may continue to benefit from nivolumab treatment beyond progression as evidenced by tumour reduction post-progression and an acceptable safety profile. (314)

Health Related Quality of Life (HRQoL) data were collected at baseline for 362 (88%) of 410 patients in the nivolumab group and 344 (84%) of 411 patients in the everolimus group. As for the FKSI-DRS score, more patients had a clinically meaningful HRQoL improvement with nivolumab (200 [55%] of 361 patients) versus everolimus (126 [37%] of 343 patients; p<0.0001). Also, the median time to HRQoL improvement was shorter in patients given nivolumab (4.7 months, 95%CI: 3.7 – 7.5) than in patients given everolimus (median not reached, NR-NR). (315)

However, many limitations have appeared with the use of PD-L1 expression as a potential biomarker for nivolumab activity, both across different tumour types and more specifically, in patients with RCC. These include the heterogeneity between primary and metastasis, as nephrectomy specimens are often used for staining and PD-L1 heterogeneity within one tumour, as high-grade areas are more likely to express PD-L1. Furthermore, PD-L1 is a dynamic biomarker, and prior exposure to VEGF inhibitor agents modulates its expression, therefore archival tissue may not be optimal for PD-L1 assessment. Finally, a mounting body of evidence underlines the limitations due to the technical methods, such as the choice of the appropriate antibody, the

specified thresholds to define positivity, and the types of cells analyzed to score the staining (immune cells *versus* tumour cells). (316)

The phase I study, checkmate 016, examined nivolumab in association with VEGFR inhibition (sunitinib or pazopanib), as well as the combination of nivolumab with ipilimumab [two regimens were assessed: nivolumab 3 mg/kg + ipilimumab 1 mg/kg (nivo3+ipi1) and nivolumab 1 mg/kg + ipilimumab 3 mg/kg (nivo1+ipi3)], in 175 mccRCC patients. Objective response rates were 38.3% and 40.4% and median PFS was 33.3 weeks and 47.1 weeks in the (nivo3+ ipi1) and (nivo1+ipi3) cohorts, respectively. Considering these results, a phase III trial is assessing the PFS and OS in patients treated with nivolumab + ipilimumab for four cycles, followed by nivolumab single agent, compared with sunitinib as first-line therapy. With the recent advancement and survival outcomes related to nivolumab and other immunotherapies, many guidelines have been updated with respect to the management of mRCC.(317-319)

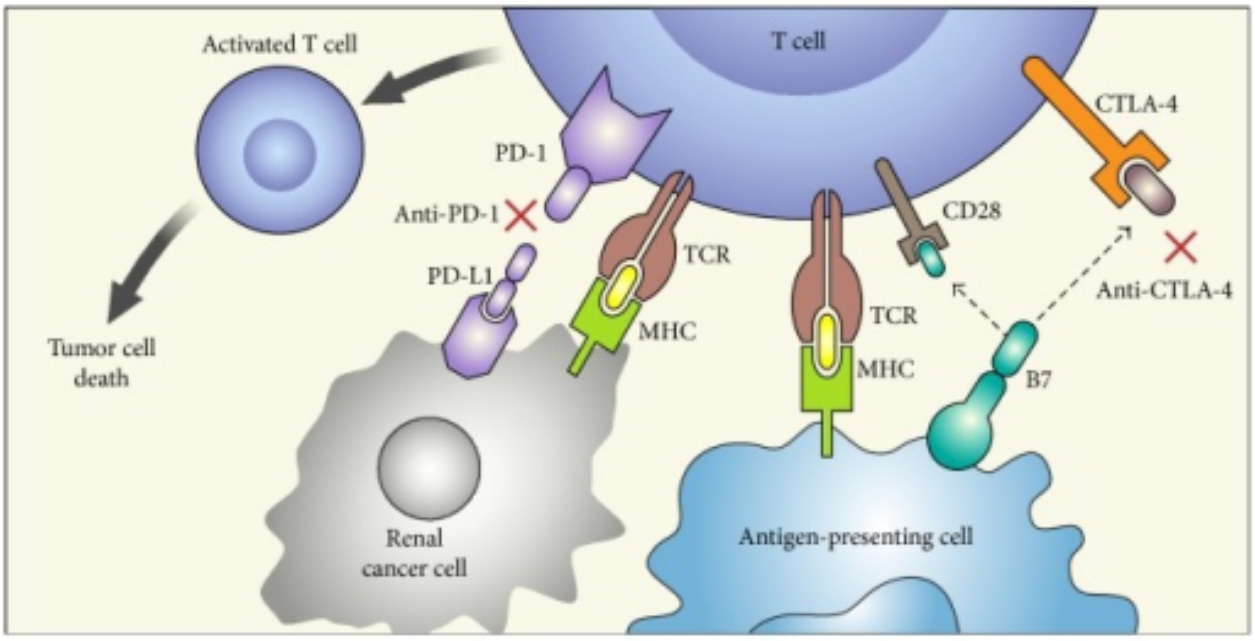


Figure 13: PD-L1 inhibitor and CTLA4 mechanism of action. (320)

Pembrolizumab

Pembrolizumab is the second anti-PD-1 inhibitor to be studied in mRCC. Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes, which may affect both tumour cells and healthy cells.(321) Pembrolizumab is under investigation in a phase 2 trial (KEYNOTE-29) in combination with ipilimumab in second-line. Additional phase 3 studies comparing pembrolizumab in combination with epacadostat or axitinib to standard of care in first-line setting are undergoing (KEYNOTE-679) and (KEYNOTE-426).(322-324) In fact, results from the KEYNOTE-426 trial have been published recently, showing a median PFS of 15.1 months (95%CI: 12.6 - 17.7) for the pembrolizumab plus axitinib arm versus 11.1 months (95%CI: 8.7 - 12.5) for the sunitinib arm (HR for disease progression or death: 0.69; 95%CI: 0.57 - 0.84; $p<0.001$). Objective response rates were 59.3% (95%CI: 54.5 - 63.9) versus 35.7% (95%CI: 31.1 - 40.4) for the pembrolizumab-axitinib and sunitinib groups, respectively ($p<0.001$). These results favor significantly this doublet, in addition to having consistent results across all risk-groups. This therapeutic option is under revision for reimbursement in Canada.(325)

PD-L1 inhibitors

Atezolizumab

Atezolizumab is an engineered humanized monoclonal anti-PD-L1 antibody that specifically inhibits PD-L1/PD-1 signalling to restore tumour-specific T-cell immunity.(326) A phase 2 study comparing atezolizumab with bevacizumab vs. sunitinib in 305 patients found an overall response rate of 18% vs 9% in patients with increased tumour expression of PD-L1. The objective response rate was 26% in all crossover patients, and the PFS was 8.8 months in all crossover patients. In the

subset of patients who were PD-L1–positive (as defined by > 1% expression of PD-L1 on tumour-infiltrating cells), progression-free survival favored the combination early on. There was a doubling of progression-free survival in the combination arm: 14.7 vs 5.5 months for atezolizumab and 7.8 months for sunitinib (a 36% improvement for the combination). (234)

Avelumab

In the same lane as atezolizumab, avelumab is a PD-L1 inhibitor under development for mRCC. It is being studied in The JAVELIN-101 trial in combination with axitinib in first-line setting.(327) In the overall population, the median progression-free survival is 13.8 months, as compared with 8.4 months (HR: 0.69; 95%CI: 0.56 - 0.84; p<0.001). Additional phase 3 studies are underway to assess to efficacy and safety of this combination in first-line setting.(328)

Ipilimumab

Ipilimumab is a monoclonal antibody that blocks the inhibitory signal by binding to CTLA-4. CTLA4 (CD152) is an inducible receptor expressed by T cells, which ligates the B7-family of molecules (primarily CD80 and CD86) on antigen-presenting cells. When triggered, it inhibits T-cell proliferation and function.(329). In first-line setting, the CHECKMATE-214 study comparing ipilimumab in combination with nivolumab vs. sunitinib showed a survival superiority for the combination. The median overall survival was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (hazard ratio for death: 0.63; p <0.001). The objective response rate was 42% versus 27% (p <0.001), and the complete response rate was 9% versus 1%. (330) The 2019 update of European guidelines (EAU and ESMO) describe the said combination as the new standard of care in low and intermediate-risk patients in first-line setting.(318, 319)

Conclusion:

The utilization of pharmacotherapy in mRCC has significantly shaped the prognosis of patients. In fact, survival statistics reflect this reality with an increase in the median 5 years survival rate from 8% to 50% in a decade. It goes without saying that the introduction of these technologies was accompanied by significant costs to innovation. The 8 molecules described above have all been introduced to the market in the past decade, with sunitinib being the first in 2007. The next year will see another significant shift in the way mRCC patients are treated with the introduction of immunotherapies and combination treatments (doublets).

The next chapter will address the economic component of mRCC, where pharmacotherapy plays an important role as the price tag continuously increases with new developments.

Chapter 3: Economic burden of mRCC

Given the governmental structure in Canada and its involvement in the healthcare system, the management of the healthcare system favours societal perspective. That being said, the economic burden and the management cost of diseases are two important factors considered systematically nowadays in any healthcare management program in Canada. The following section will depict the different methodologies used in assessing the costs related to healthcare management and the cost-effectiveness of healthcare technologies. Also, a literature review of the cost of treating mRCC will be summarized.

3.1 Decision analytic modeling for health technology assessment

Pharmacoeconomics is the study of how individuals & society end up choosing, with or without the use of money, to employ scarce resources that could have alternative uses to produce different commodities and circulate them for consumption now or in the future, among various people and groups in society. There are two common methods that economists use to evaluate value for health-related consequences: the human capital approach and the willingness-to-pay approach.(331)

The discipline of pharmacoeconomic was initiated in the late 60s with the introduction of the cost-benefit analysis looking into the inclusion of hemodialysis in the management of renal insufficiency. The cost-benefit approach translated both used resources and clinical benefits in monetary value. This capital approach was then replaced in order to take in account the opportunity cost and avoid the monetization of the human benefit.(332) Afterwards, the introduction of cost-effectiveness and cost-utility analysis was made for the assessment of new healthcare technologies with a willingness-to-pay approach.

Decision tree

Decision tree modeling is the simplest form of methods used in healthcare decision modeling. Graphically, a decision tree is compromised of a decision node (or intervention) followed by potential consequences, represented as branches with respective probabilities. It is well suited for healthcare problems that involve less recursive events. This method is not commonly used in disease modeling such as oncology since it represents fixed time periods (average time) between outcomes. Also, the inclusion of recurrence events in a decision tree model is not possible, which limits its utility in complex model involving recurrent events.(332)

Markov cohort simulation

A Markov model is a model summarizing the disease in question by different states, which are related by probabilities of transitioning and are mutually exclusive and exhaustive.

The purpose of doing a model is to extract the costs and effectiveness beyond trial data by reflecting all appropriate evidence and relevant comparators. Costs and health outcomes are combined for a modelled cohort of patients over consecutive cycles to provide a summary of the cohort experience, which can be compared with the aggregate experience of a comparable cohort, for example one receiving a different (comparator) intervention for the same disease.

Some limitations are found with the cohort Markov model. For instance, Markov model do not take no account of patient disease history and assumes uniform population, which leads to an equal and constant risk. In other words, this means the possible transitions individuals can make depend only on the state they are in, and not on how they arrived at that state. This characteristic is often known as the Markov assumption. This problem with the Markov assumption is especially highlighted in two settings. First, when more than one interpedent disease is being considered, the probability of one is often affected by the prior occurrence of another. Secondly, when model inputs (such as transition probabilities, utilities and costs) evolve over time. For example, as the age of modeled subjects increases with repeated cycles, their risks of diseases will increase (utilities and

costs) over time. In the case of RCC, as seen in the previous section, age is defined as a prognostic factor in many cases for recurrence and higher risks of mortality.

The first problem is overcome by including as many health states as is required to capture important disease combinations. However, the inclusion of too many health states into a Markov model can render it unwieldy. Paradoxically, a complex Markov model that attempts to more accurately reflect multiple related conditions may be subject to more uncertainty because of the need for more data inputs and assumptions to be made about them. The second problem of evolving data inputs is overcome by including cycle specific inputs. For some inputs, cycle specificity is easily estimated, such as age-related changes to risks of disease but for others, it poses a challenge due to a lack of data, such as age specificity of disease costs and utilities.

Markov model with patient-level simulation

Simulation of each patient seperately at a time in order to analyze their progression in the model refers to a method of undertaking multiple simulations of a model, each time taking samples from specified uncertainty ranges of the model's inputs (as opposed to point estimates). These uncertainty ranges are most often expressed as probability distributions, which describe the range of possible values for a parameter as well as the probability of each value occurring. Common types of probability distributions include 'gamma', 'uniform', 'normal' and 'triangular'. Probability distributions that relate to data inputs for a model are often called input distributions. Micro-simulation models are predominantly useful when individuals have a mix of interconnected (and potentially changing) risk factors that influence their experience of a disease over time.

Cost-effectiveness and cost-utility analysis

A pharmacoeconomic analysis compares 2 or 3 treatments for a specific disease. The 2 main metrics used to evaluate and compare alternatives are costs and effectiveness (health outcomes). Both costs and effectiveness can be defined differently from one analysis to another. In fact, health

outcomes can be quantified as disease specific (case prevented or averted infections) or generic (life years gained). In cost-utility analyses, health outcomes are defined taking in consideration quality of life, as Quality-Adjusted Life Year gained (QALY). This QALY measure is quantified between 0 and 1, as 0 being death and 1 seen as a perfect health state. QALYs are estimated by weighting survival with utility. For example, a patient living 10 years with an average 0.5 quality of life will have 5 QALYs. This method is used to highlight the marginal cost and health benefits associated with a treatment. The difference between 2 treatments used for the same indication is calculated by implying an incremental cost-effectiveness ratio (ICER), which demonstrates the total cost per additional QALY (gained) conferred by one intervention over the alternative. The ICER for two competing treatments A and B is given by:

$$ICER = \frac{(CA - CB)}{(\mathrm{EA} - \mathrm{EB})}$$

where C represents costs and E represents effectiveness. The ICER is usually reported in dollars or the currency used per QALY. There are 4 possible results when analyzing an ICER, which is usually presented between 4 quadrants. (Figure 14) The first quadrant represents an alternative that is more costly and more effective. The second quadrant presents treatments that are more costly and less effective; these are usually called dominated options. The third quadrant define treatments that are less costly but more effective, and are commonly called dominant. The fourth quadrant is less commonly seen in health technology assessments, defined as less costly and less effective.(332)

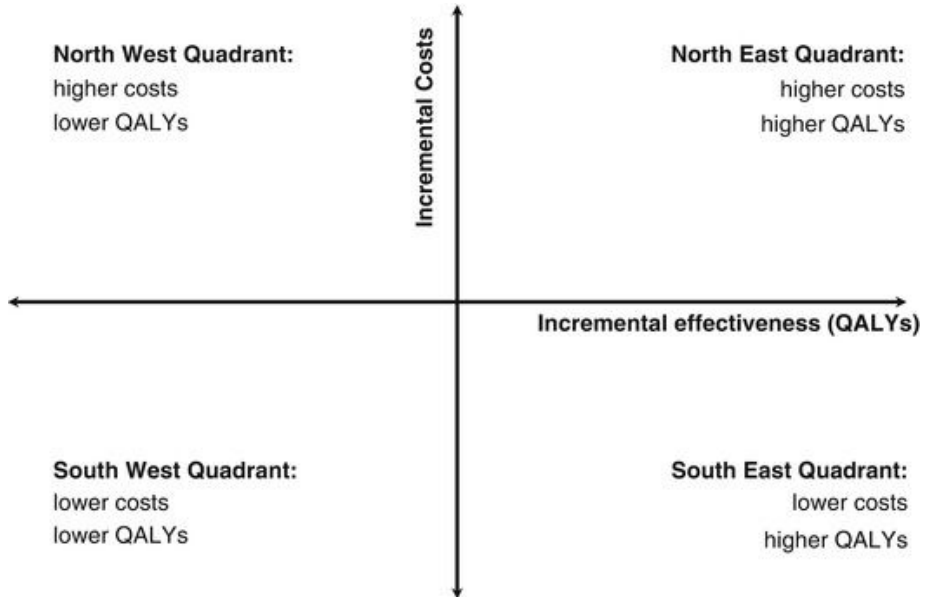


Figure 14: Incremental cost-effectiveness ratio (ICER) quandrants.

3.2 Economic evaluation of mRCC

As the health policymakers strive to make judicious use of the healthcare budget, clinical decisions and guidelines regarding the selection of appropriate treatments are increasingly relying on the evaluation of the financial burden associated with treatments.

The following section depicts the economic studies focusing solely on the cost component of mRCC. The purpose of these studies is to facilitate decision making in healthcare planning and resource allocation by underlining the economic impact of adopting a treatment on the healthcare budget. In addition, these studies help to compare different treatments from an economic and clinical perspective. The following section contains cost-description studies, cost comparison and economic analysis including pharmacoeconomic models.

3.2.1 Economic burden of mRCC

The economic burden of mRCC has not been documented extensively in Canada. In fact, very few studies have looked into the global cost of this disease. Gupta *et al.* estimated the economic burden of mRCC in 2006 and found the estimated total burden of mRCC in the United States to be around

105-556 Million $ in 2006.(333) Gupta et al. then assessed the global cost of mRCC and the estimated cost was up to 1.6 billion $ in 2006.

Many studies have compared the cost of pharmacotherapy and disease management between the early 2000 and after 2005, which marks the introduction of targeted therapy in the management of mRCC. In a Danish retrospective study, comparison of the health care cost per patient per year between 2006–2009 and 2002–2005 revealed lower inpatient costs (€11,899 vs €19,944; adjusted relative risk [RR]: 0.64), higher outpatient costs (€14,308 vs. €6,209; RR: 2.39), and higher separately calculated drug costs (€12 040 vs €3103; RR: 3.82; all $p < 0.001$) for the former era of 2000. However, the total health care cost per person per year did not differ significantly (€27 676 vs €27 856; RR: 1.05; $p = 0.5$) between the two periods.(334) In parallel, an American study analyzed 1,527 mRCC patients from 2004 until 2010 using private insurance data claims. For 767 patients receiving modern therapy who were < 65 years old and stratifying by whether the first-line treatment was oral or intravenous, drug cost per patient with ancillary services was $59,664 versus $86,518, respectively ($p < 0.001$). As per treatment costs, the authors demonstrated a higher difference in costs between 2004 and 2010 ($11,458 vs. $68,660).(335) These analyses allow us to think that the introduction of more costly therapy after 2005 is balanced by less medical expenses related to hospital management and adverse events of cytokine therapy. This being said, these analyses reflect a great example of the value of therapy beyond price.

Another interesting research objective pertaining to cost in mRCC is the difference between targeted therapies. In fact, several studies have compared the cost of treating patients with sunitinib vs pazopanib. Amdahl *et al.* assessed the healthcare resources used from patients included in the COMPARZ trial; the mean total costs for pazopanib-treated patients were 8.0% lower than those treated with sunitinib ($80,464 vs. $86,886; p=0.20). The findings suggest that health care costs

were lower among patients with advanced RCC treated first-line with pazopanib versus sunitinib because of adverse event management and a numerical longer time on treatment.(336) The authors in this publication states however that these results are influenced by the design of the clinical trials, COMPARZ, and that may not reflect what may be experienced in a real-world setting. Similarly, a retrospective study using Medicare data in the United States estimated the economic burden of elderly patients treated with pazopanib and sunitinib. Pazopanib was associated with significantly lower monthly all-cause costs compared with sunitinib ($8,845 vs $10,416, respectively), as well as lower inpatient costs associated with RCC diagnosis ($1,542 vs $2,522), fewer monthly inpatient admissions (0.179 vs 0.262), and shorter length of inpatient stay (1.375 days vs 1.883 days; all $p < 0.004$). (337)

As mentioned previously, the management of adverse events is one of the most important parameters differentiating between the cost of sunitinib and pazopanib. As a matter of fact, Hagiwara *et al.* conducted a review focusing on the cost of adverse events. Sixty-four percent of patients receiving targeted therapies for mRCC had health care encounters for >1 adverse event. Mean (SD) total costs of care during the 30-day, post event period was substantially higher among patients with versus without adverse events: $12,177 ($19,621) versus $4,070 ($8,142), respectively. Adjusting for differences in baseline characteristics, the estimated cost difference was $11,373 (95%CI: $5286 – $21,419).(338)

3.2.2 Cost-effectiveness of first-line therapy in mRCC

Several studies have looked into the cost-effectiveness of different targeted therapy by comparing similar treatments in their respective line setting. The following section summarizes the cost-effectiveness studies found in the literature in mRCC and first-line setting. Table 7 summarizes the key cost-effectiveness analysis including sunitinib and pazopanib.

Many Canadian studies have looked at the cost-effectiveness of targeted treatments in first-line

setting using mainly clinical efficacy from RCTs. Chabot *et al.* had looked at the cost-effectiveness of sunitinib compared to immunotherapy (interferon-α), as it was the standard of care. (339) A Markov model with 6 health states was included in the pharmacoeconomic analysis: progression-free survival on sunitinib or interferon-α, progression and transition to active second-line treatment followed by best supportive care (BSC) or transition directly to BSC without going through a second-line active treatment, death due to cancer, or death because of other causes.

The total lifetime costs per patient in the sunitinib arm was estimated to be $107K versus $45K in the interferon- α arm. The base case result yielded an ICER of $144K/quality- adjusted life-year gained for sunitinib compared with interferon-alfa. Probabilistic sensitivity analyses generated 90% credibility intervals of $89K–$133K per LYG, and $102K–$267K per QALY gained. The ICER found in this analysis was used for the initial HTA submission of sunitinib in Canada. Even if the ICER of 144K was above the commonly used threshold of 50-100K, given the significant difference in PFS between sunitinib and interferon- α (11 vs. 5 months), sunitinib was reimbursed by public healthcare funding in first-line setting for mRCC patients.

Benedict *et al.* compared sunitinib to sorafenib and bevacizumab (with interferon-α). Sunitinib was more effective and less costly than sorafenib (gains of 0.52 PFLYs, 0.16 LYs and 0.17 QALYs and savings/patient of $13,576 in the US) and bevacizumab plus interferon-α (gains of 0.19 PFLYs, 0.23 LYs and 0.16 QALYs in both countries and savings/patient of $67 798 and $47,264 in the US and Sweden, respectively).

Several studies in different countries have looked into the cost-effectiveness of sunitinib vs. pazopanib using the COMPARZ and PISCES trials as it is the only published RCT directly comparing both treatments. Amdahl *et al.* evaluated the cost-effectiveness of sunitinib and

pazopanib using the COMPARZ trial in 4 countries including Canada. The results were consistent between the 3 publications as the methodology and model were identical, but only adjusted for the local costs.(340-343)

The cost-effectiveness analysis completed for Canada presented a base case where pazopanib was estimated to provide more QALYs (0.059) at a lower cost (−$10,293) versus sunitinib. The probability that pazopanib yields more QALYs than sunitinib was estimated to be 79% in probabilistic sensitivity analysis. (341) Clear limitations of these analyses are the source of data for the effectiveness, as the COMPARZ study can misinterpret the real-clinical practice where dosage and schedule adjustment are often conducted. Knowing that dosage or schedule adjustments are current, this practice can influence the costs and the efficacy included in the model.

Table 7: Cost-effectiveness studies in mRCC comparing targeted therapies.

Study	Comparator	Country	Data sources	ICER	Sensitivity analysis
Amdahl *et al.* Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in the United Kingdom (341)	Sunitinib vs. pazopanib	United Kingdom (2017)	COMPARZ and PISCES trial	Pazopanib is dominant more QALYs (0.0565) and lower cost −£1,061	The probability that pazopanib is cost-effective versus sunitinib was estimated to be 96% and 95% for the threshold values of cost-effectiveness of £20,000 and £30,000 per QALY gained, respectively.
Amdahl *et al.* Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in Canada (340)	Sunitinib vs. pazopanib	Canada (2016)	COMPARZ and PISCES trial	Pazopanib is dominant more QALYs (0.059) and lower cost −$10,293	In probabilistic sensitivity analyses, pazopanib was dominant in 79% of simulations and was cost-effective in 90%–100% of simulations at a threshold cost-effectiveness ratio of CA$100,000.
Delea *et al.* Cost-Effectiveness of Pazopanib Versus Sunitinib for Renal Cancer in the United States.(342)	Sunitinib vs. pazopanib	United States (2015)	COMPARZ and PISCES trial	Pazopanib is dominant more QALYs (0.092) and lower cost − $6,828	The probability that pazopanib was more cost-effective than sunitinib was 90% for threshold values of cost- effectiveness between the range of $10,000-$160,000 per QALY gained
Benedict *et al.* Economic evaluation of new targeted therapies for the first-line treatment of patients with metastatic renal cell carcinoma(344)	Sunitinib vs. Bevacizumab + interferon-α vs. Sorafenib	United States	AVOREN trial.(232) sunitinib vs. interferon-α (Motzer et al.)(250) sorafenib vs. interferon- α (Escudier et al.) (286)	Sunitinib vs. Sorafenib (gains of 0.52 PFLYs, 0.16 LYs and 0.17 QALYs and savings/patient of $13 576) Sunitinib vs. Bevacizumab (gains of 0.19 PFLYs, 0.23 LYs and 0.16 QALYs in both countries and savings/patient of $67 798)	The probability of sunitinib providing a cost-effective alternative to sorafenib and bevacizumab plus IFN- α was 74% at a WTP of $100 000.

Calvo *et al.* Cost-effectiveness evaluation of sunitinib as first-line targeted therapy for metastatic renal cell carcinoma in Spain.(345)	Sunitinib Bevacizumab + interferon-α Sorafenib	Spain	AVOREN trial.(232) sunitinib vs.interferon- α (Motzer et al.)(250) sorafenib vs.interferon- α (Escudier et al.) (286)	Sunitinib was more effective and less costly than both SFN (gains of 0.52 PFLY, 0.16 LY, 0.17 QALY) and BEV/IFN (gains of 0.19 PFLY, 0.23 LY, 0.16 QALY) with average cost savings/patients of €1,124 and €23,218, respectively.	At a threshold of € 50,000/ QALY, the probability of sunitinib providing the highest Incremental net benefit was 75%.
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.(343)	Sunitinib vs. pazopanib	Italy	COMPARZ study and PISCES study.(251, 273)	In the base case, pazopanib was associated with higher QALYs and lower costs and dominated sunitinib.	The probability that pazopanib is cost-effective versus sunitinib was estimated to be 85% at a cost-effectiveness threshold of €20,000, 86% at a threshold of €30,000, and 81% at a threshold of €50,000 per QALY.
Chabot *et al.* How Do Cost-Effectiveness Analyses Inform Reimbursement Chabot et al. Decisions for Oncology Medicines in Canada? The Example of Sunitinib for First-Line Treatment of Metastatic Renal Cell Carcinoma(339)	Sunitinib vs. interferon- α	Canada	sunitinib vs. interferon- α (Motzer et al.)(250)	Sunitinib yielded a high cost ($62,266) but more QALYs (0.43) ICER of $144K/quality- adjusted life-year gained for sunitinib compared with interferon-alfa.	Probabilistic sensitivity analyses generated 90% credibility intervals of $89K–$133K per LYG, and $102K–$267K per QALY gained.

Remak et al. Economic Evaluation of Sunitinib Malate for the First-Line Treatment of Metastatic Renal Cell Carcinoma (346)	Sunitinib vs. interferon- α.	United States	sunitinib vs. interferon- α (Motzer et al.)(250)	The incremental cost-effectiveness ratio of sunitinib versus IFN- α was $18,611 per progression-free year gained and $67,215 per LY gained, and the cost-utility ratio is $52,593 per QALY gained.	Sensitivity analyses found the results to be most sensitive to utility values during treatment, the cost of sunitinib, and the cost of BSC. Model results were robust to changes in other model variables.

3.2.3 Health technology assessment of mRCC targeted therapies in Canada

For all of Canada, except Quebec, the Canadian Agency for Drugs and Technologies in Health "CADTH" provides evidence, analysis, advice and recommendations to health decision-makers so they can make informed decisions about reimbursement drugs through two programs: The Common Drug Review (CDR) and the Pan-Canadian Oncology Drug Review (pCODR). CDR is a specialized program for the evaluation of drugs and it issues recommendations for the reimbursement (or not) of drugs by the federal, and provincial and territorial, public drug plans, with the exception of Quebec. Thereafter, it is up to each province to rely or not on the recommendations of the CDR. The pCODR is a specialized program in the evaluation of anticancer drugs. In the same way as the CDR, the pCODR issues recommendations for the reimbursement (or not) of cancer drugs by the federal public drug plans, and the provincial and territorial governments of Canada, with the exception of Quebec. (347)

CADTH and INESSS, both health technology assessment bodies in Canada have reviewed the clinical and economic value of treatments in mRCC. Table 8 lists the recommendation based on ICER for the reviewed targeted treatments.

Table 8: Recommendation from Canadian HTA bodies for mRCC targeted therapies.

Treatment	Date of recommandations	Recommandation INESSS	Recommandation CADTH	ICER (LYG)	ICUR (QALY)	Comparator
Sunitinib	2007	list with criteria	do not list	$42,000	$56,000	Interferon alpha
Sorafenib	2006-2010	do not list	do not list	$78,000		placebo
Temsirolimus	2012	list with criteria	-			Interferon alpha
Pazopanib	2011-2013	list with criteria	list with criteria	$38,122	$57,309	Placebo
			list	Cost-effective	Cost-effective	Sunitinib
Axitinib	2013	list with criteria	List with criteria	Cost-minimization analysis		Sorafenib
Everolimus	2010	do not list	-			Placebo
Nivolumab	2016	do not list	List with criteria (condition to price reduction)		$242,521	Everolimus

As presented in the table above (Table 8), many of the Canadian recommendations were negative such as with Sunitinib and Sorafenib. The unofficial but mostly used threshold in oncology to conclude on a cost-effective therapy is 70-100k per QALY gained. Given this threshold, we can assume that most therapies would be recommended for listing, but many of these recommendations were based on studies presenting preliminary data using PFS as a surrogate endpoint. Given the weak evidence of PFS being a good predictor of OS, this led to many negative recommendations from CADTH. Another important factor to lead recommendations is the unit price of the medications. This is clearly stated in the recommendation for Nivolumab in second-line setting with an ICER of $242,521. CADTH recommended Nivolumab to be listed conditional to the cost-effectiveness ratio to be improved to an acceptable level.

Chapter 4: Use of targeted therapy in metastatic renal cell carcinoma patients: clinical and economic impact in Canadian real-life setting.

4.1 Preface

In this chapter, we assessed the effectiveness of sunitinib and pazopanib in patients with clear cell mRCC who are treatment naïve. The CKCis database was used to estimate the effectiveness. This study demonstrated the effectiveness of sunitinib, differently from RCT and differently from pazopanib. This reflects the real clinical practice in Canada.

Status: Published. Nazha S, Tanguay S, Kapoor A, Jewett M, Kollmannsberger C, Wood L, Bjarnason G, Heng D, Soulières D, Reaume N, Basappa N, Lévesque E, Dragomir A.

Use of targeted therapy in patients with metastatic renal cell carcinoma: clinical and economic impact in a Canadian real-life setting. Curr Oncol. 2018 Dec;25(6): e576-e584

Use of targeted therapy in metastatic renal cell carcinoma patients: clinical and economic impact in Canadian real-life setting

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Words: 3,232

Pages: 17

Tables: 3

Figures: 2 (1 online)

Running title: Effectiveness of sunitinib vs. pazopanib

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Funding statement: Sara Nazha has received a scholarship award from the Canadian Centre for Applied Research in Cancer Control. Dr. Dragomir obtained salary support from the Coté-Sharp Family Foundation at the McGill University Health Center. Since June 2016, she is a Fonds de Recherche du Québec - Santé (FRQS) Junior 1 Research Scholar.

***Competing interests: No authors have any competing interests to declare

Abstract presentation at the Canadian Urology association (CUA) 2017, the Canadian Centre for Applied Research in Cancer Control (ARCC) 2017 and the International Society of Pharmacoeconomic and Outcome Research (ISPOR) 2016

Abstract:

Introduction: Outside of randomized controlled clinical trials, the understanding of the effectiveness and costs associated with targeted therapies for metastatic renal cell carcinoma (mRCC) is limited in Canada. The purpose of this study is to assess the effectiveness and cost of targeted therapies for mRCC patients using real-world prospective data.

Methods: The Canadian Kidney Cancer information system (CKCis), a pan-Canadian database, was used to identify prospectively collected mRCC patients' data. First- and subsequent-line time to treatment termination (TTT) was determined from therapy initiation time (sunitinib or pazopanib) until discontinuation of therapy. Survival curves were used to estimate the unadjusted and adjusted overall survival (OS) by treatment. Unit treatment cost was used to estimate the cost by line of treatment and the total cost of therapy for the management of mRCC patients.

Results: We included 475 patients receiving sunitinib or pazopanib in first-line setting. Patients were mostly treated with sunitinib (81%) and 19% of patients were treated with pazopanib. The median TTT in first-line for sunitinib and pazopanib patients was 7.7 and 4.6 months, respectively (p<0.001). The adjusted OS with sunitinib was 32 months compared to 21 months with pazopanib. (p=0.01). In our database, pazopanib usage trended to patients who had increased age and poorer performance status. The total median cost of 1st and 2nd line treatments for patients in sunitinib and pazopanib group was $56, 476 (IQR: $23, 738 - $130,447) and $46,251 (IQR: $28,167 - $91,394), respectively.

Conclusion: The OS was significantly different between both therapies, with a higher median OS in the sunitinib group. The cost of treatments is higher in the sunitinib group, which is to be expected with a longer survival.

KEYWORDS: RENAL CELL CARCINOMA,TARGETED THERAPY,

EFFECTIVENESS, SAFETY, REAL-WORLD DATA.

4.2 Introduction

In 2016, approximately 6,200 Canadians were diagnosed with kidney cancer, with renal cell carcinoma (RCC) accounting for 90% of all patients and clear cell histology accounting for 70% of RCCs.(1, 2) While surgery remains the optimal treatment option for localized RCC, 20 to 30% of patients will present with metastasis at the time of diagnosis. In addition, over 30% of patients will develop metastatic disease at some point.(3) The prognosis for patients with metastatic disease is poor given the estimated overall 5-year survival probability rate to be less than 10%.(4, 5) Ultimately, many patients with RCC will develop metastatic disease and will require treatment with targeted therapies based on current guideline recommendations.(6-9)

In 2016, new molecular discoveries (programmed death-1/programmed death-1 ligand) led to the approval of nivolumab re-introducing immunotherapy in the treatment algorithm of mRCC.(10) These discoveries have been shown to have activity in the first-line setting in patients with mRCC, but sunitinib and pazopanib monotherapy will still be the standard of care for many Canadian patients. (6, 11, 12) Therefore, understanding the costs associated with these high cost therapies is essential.

This is especially important because, outside of randomized controlled clinical studies, the understanding of the effectiveness and costs associated with these targeted therapies for mRCC is limited in Canada. Therefore, the need for data from real-life patients exposed to these contemporary targeted therapies is growing. The purpose of this study is to assess the effectiveness and cost of targeted therapies for patients with clear cell mRCC treated with sunitinib or pazopanib in first-line setting.

4.3 Patients and methods

Eligible mRCC patients from the Canadian Kidney Cancer Information System (CKCis) database who received targeted therapy were used for our analysis. The CKCis is a multicentre collaboration of 14 academic hospitals in 6 Canadian provinces. Patient characteristics collected from CKCis include age, sex, date of RCC and mRCC diagnosis, comorbidities, and the location and number of metastases. Treatment characteristics include start date of each treatment, type of systemic therapy, dose adjustment, surgery type (nephrectomy or metastasectomy) and timing of the surgery. Clinical, demographic, imaging reports, and pathological data were obtained from patient medical records at each site and were collected up to December 2016.

Study cohort

Our study cohort consists of patients diagnosed with clear cell mRCC after January 1st, 2011 with prospectively collected data. Patients with a confirmed histological diagnosis of mRCC with clear cell subtype and receiving one of the first-line targeted therapies, sunitinib or pazopanib, were included. The index date was defined as the date of first prescription of either sunitinib or pazopanib (Figure2-Appendix). Characteristics of patients were collected from the date of diagnosis of mRCC until the end of the follow-up period. The analysis period spanned from the index date to end of follow-up, which was the earliest date between date of death, patient last visit or the end of study period (December 31st, 2016).

Statistical Analysis

Descriptive statistics were used to summarize baseline patient characteristics. Means, 95% confidence intervals (CI), medians, and interquartile range (IQR) were used to describe

continuous variables, while percentages were used to describe categorical variables. The t-test and chi-square test were used to assess differences between the sunitinib and pazopanib groups, in term of patient demographics, disease and treatment characteristics described below. First- and subsequent-line time to treatment termination (TTT) was determined from the time of the respective therapy line initiation until discontinuation of that line of treatment. The median times on 1st and 2nd line of treatment were derived from this analysis. Overall survival was determined from the index date until end of follow-up.

Effectiveness estimation

Mean and median overall survival since the initiation of first-line targeted therapy was calculated using the Kaplan–Meier curve. Cox proportional hazards model was used to examine the effect of targeted therapy controlling for demographic, disease, and treatment characteristics. Several covariates evaluated at the time of mRCC diagnosis were considered as potential predictors of progression, such as: age (under vs. over 65 years old), gender, Eastern Cooperative Oncology Group performance status (ECOG PS) at index date (0 or 1 versus > 1), metastasis location (lung, bones, liver, brain and lymph nodes), number of different metastasic locations (1 or >1), synchronous metastasis, and the timing of targeted treatment initiation following mRCC diagnosis (<1 year versus > 1 year). Surgeries such as nephrectomy before targeted treatment and metastasectomy (curative or palliative) were also included in the Cox model and were adjusted as time-dependent variables since the surgery may have been conducted after the initiation of targeted treatment. In addition, the direct adjusted survival function was used to estimate the survival curves, as well as the adjusted median and mean survivals, of the average patient in each of the groups.(13) This method estimates the direct adjusted survival function by averaging the predicted survival functions for each combination of covariates.

One-year conditional survival analysis was used to estimate the survival prognosis of patients having survived at 1-year after initiation of first-line targeted therapy. Cox regression model was used to examine the effect of variables on overall survival 1-year post-treatment initiation. Similarly, the direct adjusted conditional survival function was plotted.

Cost estimation

The unit cost of the therapies was derived from the Régie d'assurance maladie du Québec (RAMQ) list of medications. Each individual line of treatment cost was estimated by multiplying the time on treatment for each of the therapies in each line setting by the unit cost. The total cost was estimated by summing the cost of first- and subsequent-line treatments and weighted depending on the different medication used in first- (sunitinib or pazopanib) and subsequent-line (axitinib, sunitinib, pazopanib and everolimus).

All analyses were performed using the Statistical Analysis System Software (version 9; SAS Institute, Cary, North Carolina). All tests were two-sided with a significance threshold of 5%.

4.4 Results

Study population

As of December 2016, there were 1,475 patients with metastatic disease identified in the CKCis database diagnosed after January 2011; 940 of them had confirmed clear cell histology. From the cohort of 940 patients, 38% of patients (n=355) did not receive targeted treatment over the course of their disease and 110 patients were excluded from the analysis because of key missing data. Finally, our study cohort consisted of 475 clear cell mRCC patients receiving either sunitinib or pazopanib as a first-line targeted treatment. (Figure 2-Appendix)

Patient characteristics

Table 1 describes the baseline characteristics of our patient population. The median age was 63 years old and 76.2% were male. Synchronous diagnosis of metastasis and RCC patients represented 52.8% of our cohort. The median time from diagnosis of metastasis until treatment with targeted therapy was 3.4 months (IQR: 1.93 - 7). Cytoreductive nephrectomy was performed in 76.9% of patients and 19.2% of patients had a metastasectomy, whether for palliative or curative intent, throughout the course of their treatment. The most common site of metastasis was lung (53.3%), followed by the bones (19.5%), lymph nodes (22.5%), adrenal glands (11.4%) liver (7.9%) and brain (4.3%). Most patients had 1 site of metastasis (68.1%). The majority of patients had an ECOG PS of 0 or 1 (85.8%). (Table 1)

Most patients (81%) were treated with sunitinib in first-line and 19% were treated with pazopanib. Patient population was similar in both groups except for the following variables: time from diagnosis of mRCC until treatment initiation was longer in the pazopanib group (4.6 months IQR: 2.1 - 11.2) compared to the sunitinib group (3.3 months IQR: 1.9 - 6.3) *(p*=0.05), and more patients in the sunitinib arm had an ECOG PS of 0 or 1 compared to the pazopanib group (87.3 vs. 77.3 %, *p*=0.02). A difference in the median age was found between both groups (63 vs. 65) for sunitinib and pazopanib, respectively, but this difference was not statistically significant (*p*=0.09). (Table1)

Patient drug utilization

The median TTT in first-line for sunitinib and pazopanib patients was 7.7 and 4.6 months, respectively (p<0.001). Among the patients who received subsequent-line treatment (n=191), 42.4% received everolimus (n=81), 18.3% received pazopanib (n=35), 15.2% received sunitinib (n=29), 16.2% received axitinib (n=31), and 7.9% of patients received

other targeted therapies. The median treatment duration in second line was 8.04, 3.25, 3.32 and 4.14 months in the sunitinib, pazopanib, everolimus and axitinib group, respectively (p <0.001).

Survival

The median overall survival of patients treated with sunitinib was 30 months (IQR: 25 - 36 months) and 19 months (IQR: 15 - 24 months) with pazopanib (*p*=0.03) (Figure 1a). The corresponding direct adjusted median survival values were 32 months (IQR: 13-Not reached [NR]) and 21 months (IQR: 9 - 53), respectively (Figure 1b). The Cox proportional hazards regression revealed that patients treated with pazopanib presented a greater risk of death compared to patients treated with sunitinib (hazard ratio [HR]: 1.61; 95% confidence interval [CI]: 1.10 - 2.36), while adjusting for potential confounding variables (Table 2). Several other variables were associated with increased risk of death: ECOG PS equal or greater than 2 (HR: 2.05; 95%CI: 1.43 - 2.96), brain metastasis (HR 2.11; 95%CI: 1.07-4.14), and synchronous metastasis (HR: 1.50; 95%CI: 1.10 - 2.01). However, time to treatment initiation over 1 year from diagnosis of mRCC was associated with decreased risk of death (HR: 0.45; 95%CI: 0. 26 - 0.78).

The median 1-year conditional survival was 41 months (95%CI: 28-NR) vs. 12 months (95%CI: 7-NR) in sunitinib and pazopanib group, respectively (Figure 2c). Similar results were obtained for the median adjusted conditional survival; 41 months (95%CI: 13 - NR) and 13 months (95%CI: 5 - 30) for sunitinib and pazopanib, respectively (Figure 2d). When adjusted for covariables, including the ones that were not balanced between the two arms (ECOG and time to treatment initiation), patients surviving at 1-year in the pazopanib group had a higher risk of death than those in the sunitinib group (HR: 2.48; 95%CI: 1.41 - 4.36). After one year, no other variables were associated with risk of death.

Costs

As shown in Table 3, the median cost for being treated with one line of targeted therapy was $38,773 (95%CI: $14,390 - $92,532) and $19,756 (95%CI: $6,843 - $34,244) for sunitinib and pazopanib, respectively. When including up to 2 lines of targeted therapy, the total costs were $56 476 (95%CI: $23,738 - $130,447) for patients treated with sunitinib in first-line, and $46 251 (95%CI: $28,167 - $91,394) for patients treated with pazopanib in first-line. When the cost of treatment is adjusted for the survival of patients, the cost of treatment when initiated with sunitinib per month becomes lower than for pazopanib, as patients tend to live longer: $1,765/month vs. $2,202/month in the sunitinib and pazopanib group, respectively.

4.5 Discussion

Many guidelines recommend the utilization of targeted therapies in first-line setting for mRCC patients with clear cell subtype.(6-9) However, there is limited information regarding the effectiveness and cost of targeted therapies in real life for mRCC patients. Our CKCis database is unique as it provides an in-depth look at contemporary mRCC management in academic hospitals across Canada. The objective of this study was to analyze the effectiveness associated with first-line targeted therapies, comparing sunitinib to pazopanib. In addition, we estimated the actual cost of medications over the treatment period in the real-life setting.

From the 475 patients included in the analysis, most were treated with sunitinib (81%) in first-line. This disproportion is expected since pazopanib was approved in late 2011 by Health Canada, and whereas sunitinib was approved in 2007. (14) Most patients had an ECOG PS of 0 or 1 (85.8%), which is in line with eligibility criteria for access to these therapies in Canadian provinces. The number of patients with metastasis at diagnosis

(52.8%) was much higher, comparatively to numbers presented in other studies (30% on average). (1, 3, 4)

TTT in first-line was significantly different between sunitinib and pazopanib before initiation of subsequent treatment (p<0.001). This could be linked to the scheduling adjustments, which were observed mostly in the sunitinib group. In subsequent-line, TTT varied between treatments (3.25 to 8.04 months), but samples were small as only 40% of patients received a subsequent-line treatment. Several studies have looked into the TTT of subsequent line treatment with mTOR inhibitors ranging from 4.9 to 9.7 months in prospective studies and from 1.4 to 5.5 months in retrospective studies. (15-19)

A statistically significant difference of 11 months was seen between the overall survival of sunitinib and pazopanib in first-line (30 vs. 19 months, respectively). The main factor that can possibly explain this difference is dose scheduling in patients treated with sunitinib. One particular practice in sunitinib dose adjustment has patients starting on, or later transitioning to, an alternate schedule of 2-weeks-on/1-week-off (2/1) or an even more individualized dose rather than the recommended 4 weeks on with 2 weeks off. Many studies evaluated the efficacy of schedule 2/1 compared to schedule 4/2 and found similar or improved OS. In fact, Atkinson et al. demonstrated a median overall survival of 17.7 months on the traditional schedule vs. 33.0 months on alternative schedules (p <0.0001). Another Canadian study showed impressive progression free survival data when using a very individualized schedule and some of those patients would be in this study cohort as they would have been part of CKCis as well.(20) Other factors which may account for this OS difference between pazopanib and sunitinib in our CKCis database is the trend towards increased age and poorer performance status in the pazopanib group.

The effect of crossing over from one treatment to another or the use of alternative therapies after discontinuation in clinical practice may explain the difference perceived between our overall survival results and the ones reported in phase 3 RCTs and observational studies. (11, 21-26) Many variables were found to predict mortality, such as time to first-line targeted treatment less than a year. This is likely confounded by physician choice to keep patients with favorable prognosis on observation longer before initiation of targeted therapy. Other observational studies have looked into the survival of mRCC patients under targeted therapy. Morales et al. used an international retrospective database to assess the efficacy of sunitinib and pazopanib in RCC patients. The results did not demonstrate a difference in overall survival between sunitinib and pazopanib (22.3 versus 22.6 months, respectively, $p = 0.65$). This could be explained by the international nature of their database; schedule adjustment is not as common in clinical practice in other countries as it is in Canada. However, we can observe a similar decrease in the median OS of pazopanib. Another observational study conducted by Lalani et al. using the CKCis database compared the clinical efficacy of sunitinib and pazopanib. Their study differs from ours, as it did not limit the analysis to clear cell patients.(11) In addition, we looked into the effect of different potential prognostic or potentially confounding variables (such as metastasic location, ECOG score, age and time to initiation of treatment) as presented in our Cox regression analysis and analyzed the conditional survival of patients beyond one year of therapy initiation.

When conditional survival analysis was used to estimate the median overall survival of patients one year post-treatment initiation, the difference between both treatments was even greater than the difference in overall survival from the initiation of first-line therapy. The choice of therapy was the only factor associated with risk of death when analyzing

conditional survival at 1-year. Consequently, it seems that beyond 12 months of therapy, the predictive value of baseline characteristics for mortality is reduced.

The cost of treating patients with targeted therapy is substantial as the median cost of up to 2 lines of therapy was $56, 476 (IQR: $23,738 - $130, 447) for the sunitinib group, which is $10,224 higher than the pazopanib group. A recent Canadian study had estimated a very similar difference in the cost of treatment for pazopanib and sunitinib in first-line setting ($10,293).(27) It is worth mentioning that the unit prices included in our analysis reflect the drug list of the province of Quebec, which may be different from other Canadian provinces and do not reflect any product listing agreement that may be present between the manufacturers and provincial institutions.

Strengths of our analysis include the large multicenter database that focuses on patients treated with targeted therapies across several Canadian academic hospitals. Given the diverse patient population from different regions and centers, the results should reflect real-life management of mRCC in the Canadian academic setting.

Some limitations of our study are worth mentioning, such as the unbalanced proportion of patients in first-line setting between the sunitinib and pazopanib group. Our study only includes academic centers, which can be seen as a selection bias since treatment patterns and patient characteristics may be different from the community setting. In order to enable comparison with randomized controlled studies, only patients with clear cell histology were included in our study; however, it is known that targeted treatments are used in non-clear cell mRCC patients in real-life, which is not reflected in our study. (28, 29) Also to note, our study is only looking at drug costs and not the cost of other medical care such as side effect management, hospitalizations clinic visits and so forth.

These significant advances provide incremental improvement in the lives of patients, but come with high costs and face accessibility challenges in Canada. Nevertheless, even with the clinical advances of the past decade, many patients are still not responding to targeted treatment. Thus, there is still an unmet medical need in mRCC mainly due to intrinsic resistance to targeted therapies. (30, 31) Finally, Real-world evidence can provide guidance by setting benchmarks for drugs under investigation and can provide basis to understand the actual cost related to the utilization of pharmacotherapy.

4.6 Conclusion

This analysis confirms the efficacy of pazopanib and sunitinib in first-line setting using real-world data, with better overall survival observed in the sunitinib group. Finally, since pharmacotherapy in mRCC is expanding as well as its costs, additional studies covering the whole disease spectrum in the real-life setting should be conducted to optimize mRCC management.

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4.8 Tables & Figures

Table 1: Descriptive characteristics of mRCC patients undergoing first-line therapy.

Characteristics	All patients N=475	Sunitinib N=395	Pazopanib N=80	p-value
Sex, Male (%)	76.2	76.9	72.5	0.39
Median Age (IQR)	63(56-70)	63 (56-70)	65 (57-75)	0.09
Time from diagnosis of RCC to metastasis months, median (IQR)	2.1 (0-17.5)	1.5 (0-15.4)	6.1(0-29.9)	0.21
Time from diagnosis of metastasis to first-line treatment, months, median, (IQR)	3.4 (1.9-7)	3.3(1.9-6.3)	4.6 (2.1-11.2)	**0.05**
Synchronous mRCC	52.8	54.7	43.8	0.08
Nephrectomy before T.T. (%)	76.9	76.7	85.0	0.13
Metastasectomy (%)	19.2	20.0	17.5	0.60
Sites of metastasis				
Lung (%)	53.3	54.5	47.4	0.26
Adrenal Glands (%)	11.4	11.1	12.8	0.67
Bone (%)	19.5	19.8	18	0.70
Liver (%)	7.92%	8.74%	3.85%	0.06
Lymph nodes (%)	22.5	21.3	28.8	0.22
Brain (%)	4.3	4.6	2.6	0.32
ECOG				
0 (%)	37.6	39.2	29.1	
1 (%)	48.2	48.1	48.1	
≥ 2 (%)	16.1	12.7	22.8	**0.02**
Number of organs with metastases±				
1 (%)	68.1	67.9	69.2	
2 (%)	22.7	23.4	19.2	
≥ 3 (%)	9.2	8.7	11.5	0.72
Year of mRCC diagnosis (%)				
2011	7.8	9.4	0	**<0.0001**
2012	20.6	23.8	5.0	
2013	20.2	21.0	16.3	
2014	21.9	20.8	27.5	
2015	18.7	15.9	32.5	
2016	10.7	9.1	18.8	

*Defined as less than 3 months between initial diagnosis of RCC and diagnosis of metastasis
±Patients could have lesions at more than one site.

Table 2 : Cox regression model

					Conditional Cox regression analysis			
Variables	Univariate HR	*P value*	Multivariate *HR*	*P value*	Univariate HR		Multivariate *HR*	*P value*
Overall Survival								
Pazopanib (ref: sunitinib)	1.47 (1.02-2.14)	0.04	1.61 (1.10-2.36)	<0.01	2.31 (1.36-3.93)	<0.01	2.48 (1.41-4.36)	**<0.01**
High ECOG ≥ 2 (ref: 0-1)	2.30 (1.63-3.25)	<0.01	2.05 (1.43-2.96)	<0.01	1.42 (0.76-2.66)	0.27	1.38 (0.71-2.66)	0.33
Age ≥65 (ref: age≤65)	1.04 (0.79-1.37)	0.76	0.85 (0.61-1.18)	0.33	1.44 (0.97-2.13)	0.07	1.44 (0.95-2.17)	0.09
Male (ref: female)	1.02 (0.75-1.41)	0.88	0.90 (0.61-1.34)	0.61	1.37 (0.84-2.24)	0.21	0.67 (0.40-1.13)	0.13
Synchronous (ref:Metachronous)	1.50 (1.14-1.98)	<0.01	1.50 (1.10-2.01)	<0.01	1.22 (0.82-1.81)	0.32	1.21 (0.81-1.83)	0.35
Nephrectomy *	0.68 (0.48-0.97)	0.03	0.97 (0.66-1.43)	0.87	0.54 (0.28-1.03)	0.06	0.91 (0.42-1.95)	0.80
Time to treatment initiation over 1 year (ref: less than 1 year)	0.48 (0.28-0.81)	0.005	0.45 (0.26-0.78)	<0.01	0.67 (0.34-1.33)	0.67	0.55 (0.26-1.16)	0.12
Bones metastasis	1.36 (1.00-1.86)	0.05	1.43 (0.99-2.06)	0.06	1.51 (0.98-2.34)	0.06	1.55 (0.92-2.60)	0.10
Liver metastasis	0.84 (0.50-1.41)	0.50	0.99 (0.56-1.75)	0.98	0.88 (0.43-1.82)	0.74	1.02 (0.47-2.23)	0.96
Lung metastasis	0.96 (0.73-1.26)	0.76	1.11 (0.80-1.54)	0.54	0.85 (0.57-1.25)	0.41	1.03 (0.65-1.63)	0.90
Brain metastasis	1.52 (0.80-2.87)	0.20	2.11 (1.07-4.14)	0.03	1.07 (0.34-3.37)	0.20	1.78 (0.52-6.10)	0.36
Prior metastasectomy*	0.70 (0.47-1.05)	0.08	0.96 (0.59-1.57)	0.88	0.64 (0.38-1.06)	0.08	0.70 (0.41-1.21)	0.21
Number of metastatic locations ≤ 1 (ref: ≥2)	0.94 (0.70-1.24)	0.65	1.03 (0.75-1.40)	0.87	1.01 (0.67-1.53)	0.96	1.03 (0.66-4.36)	0.90

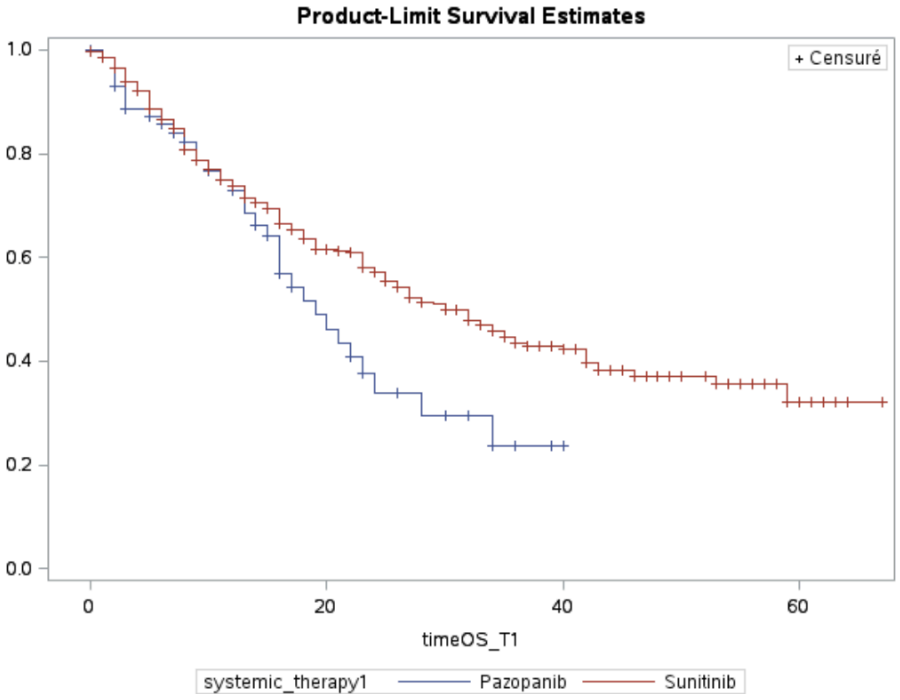
*Having a nephrectomy or a metastasectomy was analyzed using time-dependent analysis.

Table 3: Duration and Cost of targeted therapies by line of treatment (CAD $)

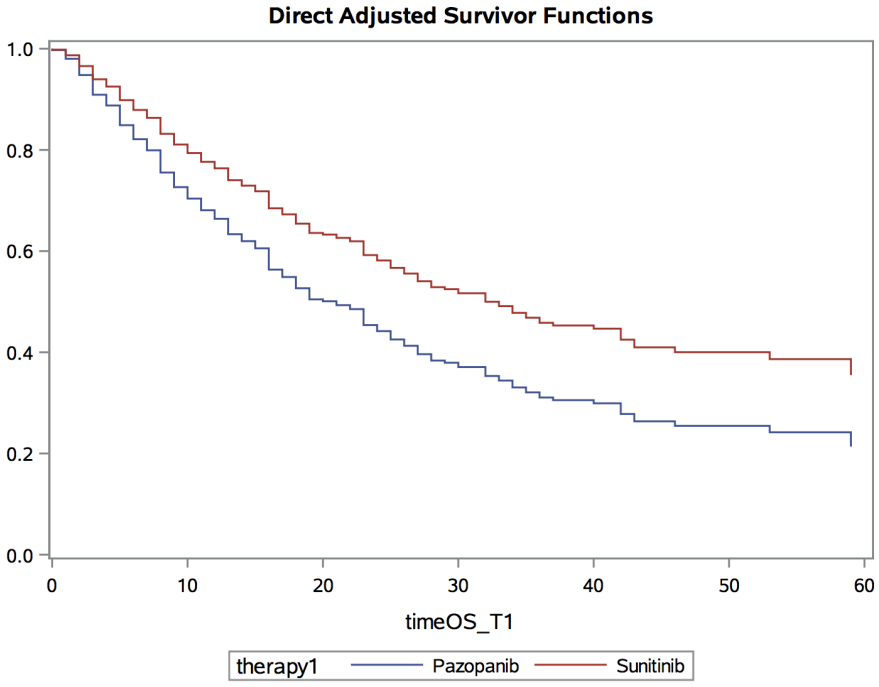
First-line therapy	Subsequent-line therapy	Treatment cost of initial therapy						Subsequent-line therapy	Treatment cost of subsequent therapy					
		Mean	95%CI		Median	IQR			Mean	95%CI		Median	IQR	
Sunitinib (n=385)	Axitinib (n=26)	77 291 $	49 865 $	104 663$	47 743 $	23 659 $	111 772 $	Axitinib (n=26)	30 727 $	21 717 $	39 893 $	25 935$	15 051$	44 788$
	Everolimus (n=75)	56 814 $	44 666 $	68 909$	35 595 $	18 938 $	82 224 $	Everolimus(n=75)	29 529 $	22 238 $	36 872$	17 290$	9 843$	36 456$
	Pazopanib (n=34)	30 873 $	21 961 $	39 733$	22 068 $	11 511$	47 955 $	Pazopanib (n=34)	24 934 $	15 184$	34 685 $	12 525 $	3 853$	37 113$
	No treatment (n=240)	72 675 $	61 801 $	83 126$	41 377 $	12 784 $	100 420 $	No treatment (n=240)						
	Weighted average	65 862 $	53 841 $	77 586$	38 773 $	14 390 $	92 532 $	Weighted average	28 370$	20 218 $	36 583 $	17 703$	9 348$	37 915$
	Total cost of sunitinib and subsequent therapy								**94 232 $**	**74 059 $**	**114 169 $**	**56 476$**	**23 738$**	**130 447$**
Pazopanib (n=90)	Axitinib (n=6)	37 421 $	20 646 $	75 729$	28 904 $	13 334 $	47 904$	Axitinib (n=6)	14 946$	- $	29 893 $	7 968 $	7 603$	20 102$
	Everolimus (n=13)	33 529 $	16 070 $	47 133$	31 794 $	14 452 $	41 969 $	Everolimus (n=13)	29 946 $	7 499 $	52 444$	18 123$	12 811$	24 946$
	Sunitinib (n=14)	9 442 $	5 356 $	13 527$	7 845 $	4 393 $	11 831 $	Sunitinib (n=14)	69 439 $	33 314$	105 565$	42 650$	35 436$	103 815$
	No treatment (n=57)	27 285 $	18 074 $	36 535$	18 498 $	4 740 $	36 130 $	No treatment (n=57)						
	Weighted average	26 317 $	16 026 $	37 523$	19 756 $	6 843 $	34 244 $	Weighted average	43 683 $	16 916 $	70 470 $	26 495$	21 324$	57 150$
	Total cost of pazopanib and subsequent therapy								**70 000 $**	**32 942$**	**107 993 $**	**46 251$**	**28 167$**	**91 394$**

Figure 1: Survival Curves

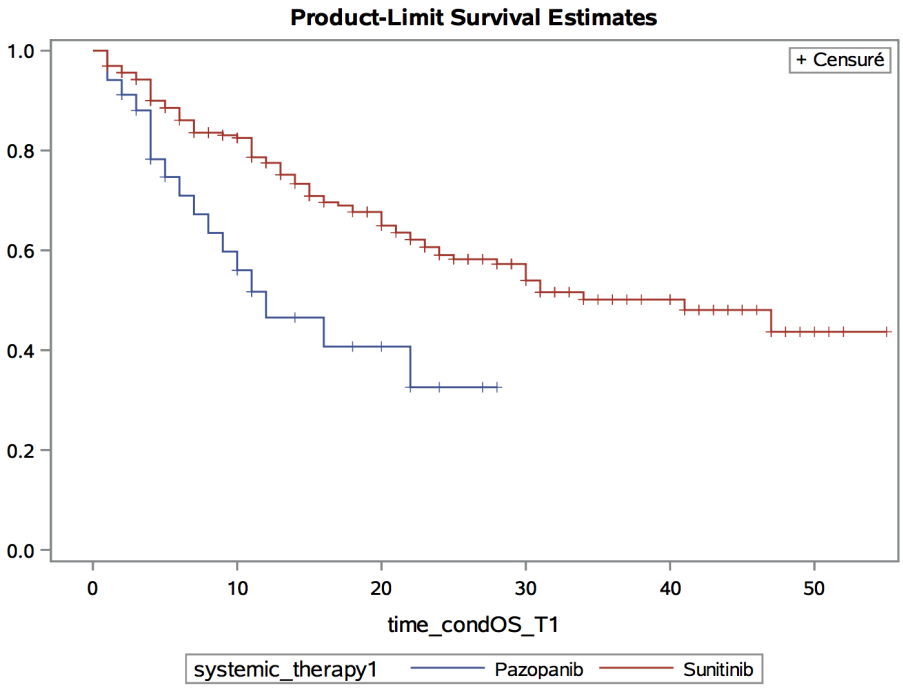
1a) Kaplan-Meier curves



1b) Adjusted survival curves



1c) Conditional survival curves



1d) Adjusted conditional survival curves

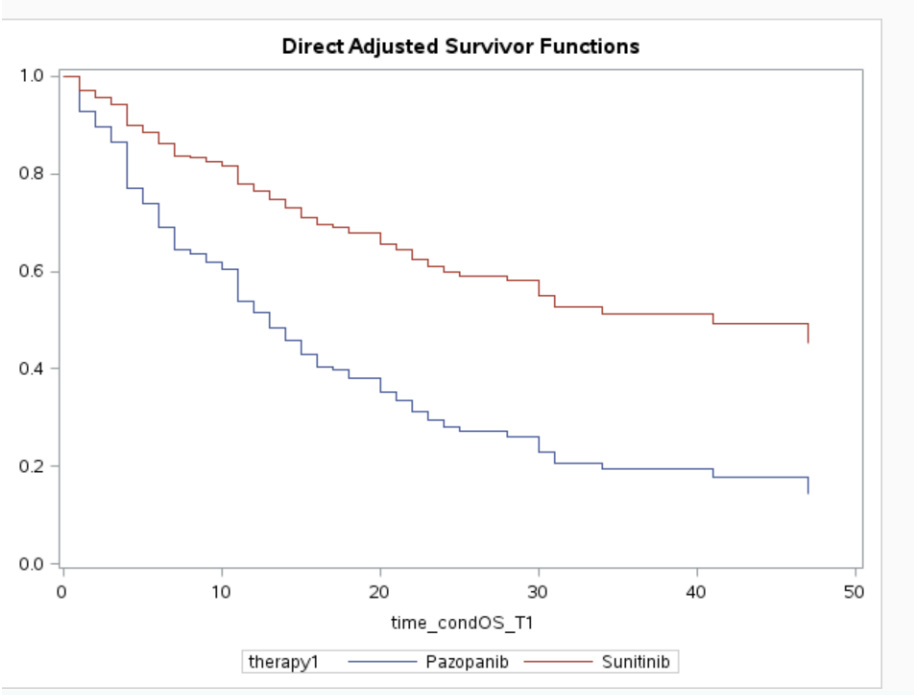


Figure	Sunitinib Median OS	95%CI	Pazopanib Median OS	95%CI	P value
a) Kaplan-Meier curve	30	25-36	19	(15-24)	0.03
b) Adjusted curve	32	(13-NR)	21	(9-53)	0.01
c) Conditional survival curve	41	(28-NR)	12	(7-NR)	0.02
d) Adjusted conditional survival curve	41	(13-NR)	13	(5-30)	0.01

NR : Not reached

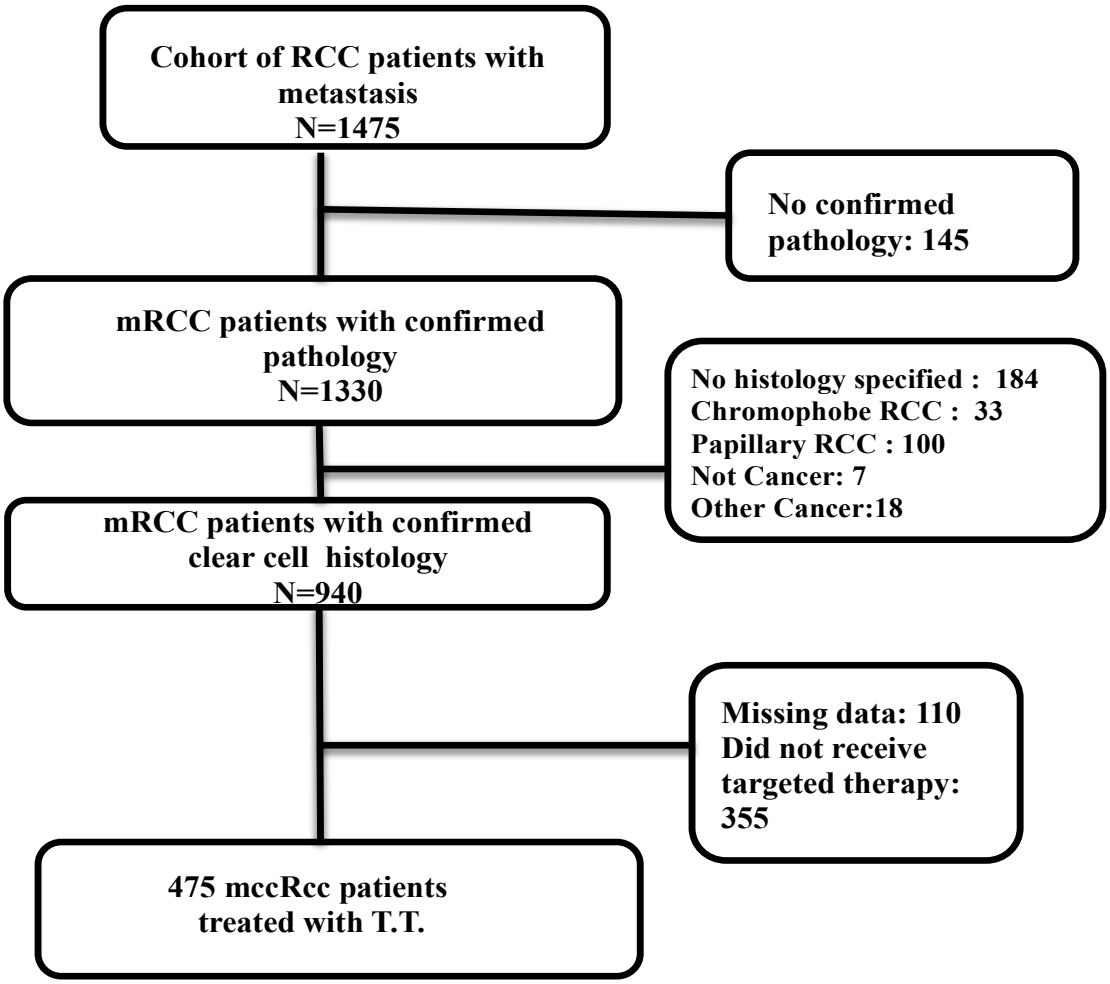


Figure 2 : Flow Chart

Chapter 5: Cost-utility of sunitinib vs. pazopanib in metastatic renal cell carcinoma in Canada using real-world evidence.

5.1 Preface

HTA bodies in Canada rely greatly on cost-effectiveness analyses to compare and recommend the utilization of medications in their respective disease area. As HTA are usually completed in the first year of the medication's introduction to the market, they usually include RCT data to present clinical efficacy. In this study, we conducted a cost-effectiveness analysis including real-world effectiveness of sunitinib and pazopanib. Clinical effectiveness was taken from the first objective of this project titled "The effectiveness of sunitinib or pazopanib in first-line mRCC patients using real-world data"

As new modalities will eventually be introduced in the management of mRCC, this study can inform HTA bodies on the cost-effectiveness of the current standard of care.

Status: Published. Nazha S, Tanguay S, Kapoor A, Jewett M, Kollmannsberger C, Wood L, Bjarnason GAG, Heng D, Soulières D, Reaume MN, Basappa N, Lévesque E, Dragomir A. *Cost-utility of Sunitinib Versus Pazopanib in Metastatic Renal Cell Carcinoma in Canada using Real-world Evidence*. Clin Drug Investig. 2018 Dec;38(12):1155-1165.

Cost-utility of sunitinib vs. pazopanib in metastatic renal cell carcinoma in Canada using real-world evidence.

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Word count: 3,472
Tables: 5
Figures: 3
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Abstract

Background and objective: The development of new targeted therapies in kidney cancer has shaped disease management in the metastatic phase. Our study aims to conduct a cost-utility analysis of sunitinib vs. pazopanib in first-line setting in Canada for metastatic renal cell carcinoma (mRCC) patients using real-world data.

Methods: A Markov model with Monte-Carlo microsimulations was developed to estimate the clinical and economic outcomes of patients treated in first-line with sunitinib vs. pazopanib. Transition probabilities were estimated using observational data from a Canadian database where real-life clinical practice was captured. The cost of therapies, disease progression, and management of adverse events were included in the model in Canadian dollars. Utility and disutility values were included for each health state. Incremental cost-utility ratio (ICUR) and incremental cost-effectiveness ratios (ICER) were calculated for a time horizon of five years, from the Canadian healthcare system perspective.

Results: The cost difference was $36,303 and the difference in quality-adjusted life year (QALY) was 0.54 in favour of sunitinib with an ICUR of $67,227/QALY for sunitinib vs. pazopanib. The major cost component (56%) is related to best supportive care (BSC) where patients tend to stay for a longer period of time compared to other states. The difference in life years gained (LYG) between sunitinib and pazopanib was 1.21 LYG (33.51 vs. 19.03 months) and the ICER was $30,002/LYG. Sensitivity analysis demonstrated the robustness of the model with a high probability of sunitinib being a cost-effective option when compared to pazopanib.

Conclusion: When using real-world evidence, sunitinib is found to be a cost-effective treatment compared to pazopanib in mRCC patients in Canada.

Key points:

- The real-world utilization and effectiveness of sunitinib and pazopanib has been noted in several studies.
- Assessing the cost-effectiveness of sunitinib vs. pazopanib in mRCC patients considering real-world effectiveness has not been published previously.
- This study will allow for better interpretation of the economic value of these targeted therapies and provide a benchmark to future treatment, which will be compared to these standards of care from an economic perspective.

Keywords: metastatic renal cell carcinoma; kidney cancer; targeted treatment; Markov model; cost of drugs;

5.2 Introduction

Renal cell carcinoma (RCC) is the third most prevalent urologic cancer in Canada following prostate and bladder cancer. The mean age of diagnosis is 62 years and 75 % of patients are male.(333) In Canada, the incidence of RCC has been increasing since 1990, which may be linked to better diagnosis techniques and the aging population.(41)

Over 35% of patients eventually progress to the metastatic phase and are treated with pharmacotherapy as part of the management of their disease.(348) In first-line setting, sunitinib and pazopanib are recommended for the treatment of metastatic renal-cell carcinoma (mRCC) of clear cell subtype.(195) The primary mechanism of action of sunitinib and pazopanib is through their anti-angiogenic properties via inhibition of the intracellular tyrosine kinase of the vascular endothelial growth factor receptor (VEGFR).(239) This action results in the inhibition of angiogenesis by decreasing activation of pathways involved in cell proliferation, cell survival, vascular permeability and cell migration.(26, 239, 349)

Both drugs have been studied in the head-to-head prospective COMPARZ trial, which concluded pazopanib to be non-inferior to sunitinib based on progression-free survival (PFS) (8.4 vs. 9.5 months; hazard ratio (HR) 1.05; 95% confidence interval (CI): 0.90 – 1.22) and overall survival (OS) (28.4 vs. 29.3 months; HR: 0.92; 95%CI: 0.79 – 1.06) with better health-related quality of life scores with pazopanib.(251) Following clinical and economic evaluation by the pan-Canadian Oncology Drug Review (pCODR) and the *Institut national d'excellence en santé et services sociaux* (INESSS), pazopanib received approval for public reimbursement in all the Canadian provinces, as an alternative treatment to sunitinib in first-line treatment of mRCC.(350) Contemporary real-world data demonstrated a significant difference in the OS of patients treated

with these targeted therapies in Canadian academic centers. In fact, the median OS for sunitinib and pazopanib were 31.7 and 20.6 months, respectively (p=0.028).(351)

With new treatments underway, sunitinib and pazopanib will be compared to innovative treatments from a clinical and economic standpoint. In fact, many immunotherapy treatments are under review for the treatment of mRCC in first or second-line setting. For example, ipilimumab and nivolumab, were studied in first-line setting for mRCC patients in the Checkmate 214 phase 3 randomized controlled trial and showed an improvement in response rates and progression free survival in intermediate and poor risk mRCC patients compared to sunitinib.(352) One of the main challenges of gaining access and use for new therapies is the cost of treatment. With an average monthly price tag of targeted agents for mRCC ranging from approximately $4,000 to $6,000, this leads to high incremental cost-effectiveness ratios (ICER) and significant budget impacts.(353) In many countries, decision-makers responsible for allocating scarce resources amongst competing treatments increasingly rely on formal economic evaluations to determine the optimal economic value of therapies. Generally, these economic evaluations are based on clinical trial data, which contain uncertainty related to the effectiveness of treatments, the real-life disease management as well as on survival beyond the end of the clinical trial period.

In addition, published studies that have looked into the cost-effectiveness of pazopanib vs. sunitinib were also based on data from randomized controlled trials to estimate the OS and the utilization of targeted therapy. Using prospectively collected real-world data; our analysis will estimate more accurately the actual value of sunitinib and pazopanib from a healthcare perspective in real clinical practice. (340, 342) Thus, the aim of our study is to evaluate the cost-effectiveness and cost-utility of sunitinib compared to pazopanib as first-line treatment for mRCC patients from

the perspective of the Canadian healthcare system, based on current practice in Canadian academic hospitals.

5.3 Methods

Model design and population:

A cost-effectiveness/cost-utility analysis was completed to evaluate sunitinib and pazopanib in first-line setting for patients with clear cell mRCC. The study was performed using a modeling approach. A Markov model with Monte-Carlo microsimulations was developed to simulate the evolution of disease since the start of first-line targeted treatment (sunitinib or pazopanib) and the management of patients with mRCC using targeted therapies. The model produces estimates for OS and associated costs by group of treatments. The population studied in this analysis are mRCC patients treated with targeted therapy (sunitinib or pazopanib) in first-line with confirmed clear cell histology. The mean age of patients is 64 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. This model was developed in order to capture the history of a patient's journey once diagnosed with metastatic disease and treated with first-line targeted treatment. It consists of distinct health states, which represent clinical events in disease progression and does not permit the patient to return to the previous state. The health states are defined as treatment-related health states since the sequence follows treatment lines used in disease management. A four-state model was developed to assess the cost-effectiveness/cost-utility of sunitinib vs. pazopanib (Figure 2). The health states are defined as follows: 1) Progression-free (defined as the initiation of pazopanib or sunitinib); 2) Progression treated with second-line therapy (initiation of a second-line treatment such as axitinib, everolimus, pazopanib or sunitinib); 3) Progression managed with best supportive care (BSC) – defined as symptom management and standard routine care; and 4) Death. Each cycle in the model corresponded to one month and the

time horizon was 60 months, which is a realistic representation of disease duration.(354) The analyses were completed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines and the Markov model was developed using TreeAge PRO healthcare software (2017 R1.1).(355)

Data sources and Transition probabilities

The transition probabilities were estimated using the survival curves and the time to treatment termination (TTT) of patients included in the Canadian Kidney Cancer Information System (CKCis) database treated with sunitinib or pazopanib in first-line setting. The CKCis is a database including 15 academic centers across Canada and among six Canadian provinces, where patients with RCC were followed for disease management. Patient information was collected prospectively since 2011 and up to December 2016 for the analysis of this project, which included baseline demographic, clinical, and laboratory data. Our research group described the CKCis database in more details in other publication such as Nazha *et al*. and Lalani *et al.(351, 356)* The project was approved by the Research Ethics Board of each individual participating centers and all patients provided consent for entry into CKCis

OS was defined as the time from initiation of first-line therapy to death from any cause, and TTT was defined as time from initiation of first-line therapy to date of discontinuation or death, whichever occurred first. The OS was adjusted for potential confounding variables using the direct adjusted survival function; this method estimates the OS by averaging the predicted survival functions for each combination of covariates.(357) We used this method to take in consideration possible selection bias of our database between patients being treated with pazopanib and sunitinib. The decision to start sunitinib or pazopanib and choice of specific agent was at the discretion of

the treating physician. Treatment-associated toxicities were defined and evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0, where CKCis captures reasons for dose-modification based on toxicities.

From the 475 patients analyzed from the CKCis database, the median age was 63 years old and 76.2% were male. Most patients (81%) received sunitinib as their first-line therapy and 19% received pazopanib. Generally, patients' characteristics were balanced between both groups, but some variables were different. In fact, patients in the pazopanib group had more poor performance status (22.8% had an ECOG of >2 compared to only 12.7% in sunitinib group) and the time from diagnosis until initiation of treatment was longer in the pazopanib group (4.6 months versus 3.3 in sunitinib group, p=0.05). Patients were followed up for a median time of 17 and 21 months in the pazopanib and sunitinib groups, respectively. Concomitant synchronous metastasis represented 52.8% of patients in our cohort. Only clear-cell carcinoma patients were included in our analysis. The median adjusted overall survival found in our database was 32 months (IQR: 13 - Not Reached) for sunitinib and 21 months (IQR: 9 - 53) in pazopanib patients. (Supplementary material) The Kaplan-Meier curves were adjusted for ECOG score, being aged over 65-year-old, time to treatment initiation, diagnosis of RCC in concomitance with metastasis and the type of therapy given (sunitinib or pazopanib) over a 5-year time period. The median TTT in first line for sunitinib and pazopanib patients was 7.7 and 4.6 months, respectively (p<0.001). The curves are found in the electronic supplementary material. The TTT for the subsequent line of treatment ranged from 3.25 and 8.04 months and only 40% of patients were treated with second-line therapy. The observed OS and TTT curves were converted using time-dependent monthly probabilities for each transition probability (Table 1). In addition, the rate of adverse events was taken from the previously published observational study based on CKCis patients and was included in the model

to account for treatment-related toxicities.(252) Mucositis, liver toxicity, hand-foot syndrome and gastrointestinal reflux disease (GERD) were included in the model based on their high incidence (Table 2).

The incremental cost utility ratio (ICUR) was calculated by dividing the difference in cost and the difference in quality-adjusted life years (QALYs) between sunitinib and pazopanib. QALYs represent the incremental gain in life years at perfect quality of life defined as a utility of 1. As for the incremental cost-effectiveness ratio (ICER), it was calculated using the difference in life years gained (LYG) over the difference in cost.

Cost

The unit cost of the therapies were derived from the *Régie d'assurance maladie du Québec* (RAMQ) list of medications.(353) The costs for each health state (first-line, second-line [progressive disease treated with second-line treatment], and progressive disease treated with BSC) were estimated by using TTT in each line of therapy based on results from the database. Other medical costs such as routine care ($770/month), management of progressive disease ($8,043) and BSC ($960/month) were included in the model from previously published literature.(339, 353, 358) Costs and outcomes were discounted at a rate of 1.5%, as per Canadian guidelines.(354) All costs were assigned in 2017 Canadian dollars ($) (Table 3). The cost of managing adverse events was extracted from Canadian studies and ranged from $850 to $3,358 (Table 2).(359)

Utility

The effectiveness of each management option was assessed by QALYs gained over the 5-year time-horizon. Utility weights assigned to each health state reflected quality of life associated with the disease in that health state and were extracted from published trials (Table 1). (339, 340)

Patients treated with sunitinib in first-line had a utility of 0.6832 vs. 0.7089 when treated with pazopanib. The utility of being in progression (second-line) and BSC was 0.6309 and 0.5509, respectively. The disutility of adverse events associated with the management options was derived from the literature and were specific for each adverse event included in the model (Table 3). (359-361)

Sensitivity analyses

In order to quantify the overall uncertainty of the model's estimates, a probabilistic analysis was performed using a Monte Carlo simulation of 1000 iterations. Furthermore, to identify key model parameters and the extent of their influence on results, one-way deterministic sensitivity analyses were conducted using the mean 15% deviation. Duration of treatment until discontinuation, cost of therapy, transition probabilities between states, time horizon and utility values were included to investigate their independent effects on the ICUR/ICER results. In addition, the model was assessed with equal utilities in the pre-progression state, whether the patient was treated with sunitinib or pazopanib. Internal validation as well as face validity was completed. This validation is useful in examining the extent to which the mathematical calculations are performed correctly in the model and are consistent with the model's specifications.(362)

5.4 Results

The 5-year total cost per patient in the sunitinib group is $107,221 with an estimated median OS of 33.51 months. The total cost difference between both strategies is $36,303 with pazopanib costing $70,918 for an estimated survival of 19.03 months. The major cost component is the progression to BSC where patients tend to stay for a long period of time. In fact, 56% and 53% of costs are linked to this health state in the sunitinib and pazopanib group, respectively. The second largest cost input is the first-line treatment, which accounts for 34% of all costs for both sunitinib

and pazopanib. The cost of the progressive state treated with second-line was similar for the sunitinib group ($8,553) and pazopanib group ($7,801) (Table 4).

The cost-utility analysis shows a difference in QALY of 0.54 in favour of sunitinib vs pazopanib (1.54 vs. 1.00). The ICUR of sunitinib vs. pazopanib is $67,227/QALY. The LYG with sunitinib is 1.21 LYG (33.51 vs. 19.03 months) and the ICER ratio is $30,002/LYG (Table 4). The cost-utility analysis resulted in a higher cost/QALY ratio, because survival with metastatic disease is usually associated with a reduced quality of life.

SENSITIVITY ANALYSIS

The deterministic sensitivity analysis is presented in Table 5. Many parameters were included in this univariate sensitivity analysis to evaluate their impact on the base-case results such as cost inputs, utility inputs, model parameters and transition probabilities. The most important input in the model was the cost of sunitinib. Decreasing the price by 15 % was related to an 18% decrease in the ICUR ($48,409/QALY). Utility values that were assigned to each health state were also important. The utility of BSC was the most important utility parameter, followed by the utility of sunitinib treatment, as they affected the ICUR by 14% and 12 %, respectively. For the transition probabilities, transitioning from BSC to death when being treated with sunitinib was the most important efficacy input. Time horizon of 3, 7 and 10 years changed the ICUR of 1%, -4% and -7 %, respectively. (Figure 2) Probabilistic sensitivity analyses showed a high probability of sunitinib being cost-effective vs. pazopanib for a willingness-to-pay (WTP) threshold of $100,000 per QALY gained, as most values were found under the WTP threshold. (Figure 3)

5.5 Discussion

Given the high economic burden of innovative therapies in oncology, cost-effectiveness/cost-utility analyses are valuable tools in the allocation of healthcare resources. In addition, the past

decade has been very fruitful in the development of new therapies for mRCC with over 8 molecules approved by Health Canada as of May 2016. In mRCC, this is the first study estimating the cost-utility of sunitinib vs. pazopanib in Canada based on real-life utilization, which should be the closest illustration of real-life practice and the most accurate estimation of the costs engendered.

The ICUR found in our analysis was $67,227/QALY and the ICER was $30,002/LYG. These ratios are acceptable given the standard thresholds to be around $50,000-$100,000/QALY in the field of oncology. The difference in cost found between sunitinib and pazopanib in first-line setting is mainly driven by the longer time to treatment failure in patients using sunitinib in first-line. When looking at the OS (33.51 months) for sunitinib, we realize that patients reside a significant time in the BSC state, which explains its high sensitivity in the deterministic sensitivity analysis.

The sensitivity analyses demonstrated the robustness of the base-case findings despite variations in key input parameters. The main inputs affected by the model are the cost of drugs and the utility values, mainly in the BSC state. As explained previously, patients seemed to spend significant time in this state.

Amdahl *et al.* have published a cost-effectiveness analysis comparing sunitinib to pazopanib in Canada.(340) The main difference between their study and ours is the source of evidence for the efficacy parameter. The authors used the COMPARZ study to estimate the transition probabilities, which is different from the prospective, observational data used in our study.(251) In fact, our base-case results are not consistent with the results of Amdahl *et al*. since the survival curves used in our analyses demonstrated a statistically significant difference in the median OS between sunitinib and pazopanib of 11.1 months (p=0.028).(252) In the COMPARZ study, the OS between both treatments was found to be very similar in the ITT analysis (28.4 vs. 29.3 months). The main

factor explaining this difference is related to the dose scheduling found in real-world practice, which was not captured by Amdahl *et al*. The relation between dose and schedule adjustment and longer survival has been underlined in multiple studies.(257, 259, 363) For instance, Atkinson *et al.* demonstrated a 15.3 months (p<0.0001) difference in OS between the traditional and alternative schedules. In addition, Bjarnason *et al.* demonstrated the benefits with individualized sunitinib therapy with an incremental 9 months of survival.(364) Another difference between our study and Amdhal *et al.* is that the survival curves used in our model were adjusted for possible confounding variables predicting mortality. In this case, we decreased the effect of potential selection bias that could be present in our observational database in order to compare sunitinib and pazopanib adequately.

Following the economic evaluation of pazopanib vs. sunitinib in first-line setting, pCODR and INESSS concluded pazopanib to be a cost-effective option assuming similar efficacy and standard dosing of the two therapies.(365) This recommendation was based on the cost-effectiveness analysis submitted by the manufacturer, where the COMPARZ and PISCES studies were used to compare the efficacy between sunitinib and pazopanib.(251, 273) In their conclusion, the pCODR report mentions the need for future research to "provide a more accurate reflection of real-world cost-effectiveness and improve estimates of budget impact".(365) Using real-world data, our study was conducted with that goal in mind and real-world evidence of the cost-effectiveness of these therapies was generated.

Some limitations of our study should be mentioned. First, despite our adjusted curves for unbalanced characteristics, some confounding might be present that we are unable to adjust for, such as comorbidities that may affect patient's survival. In addition, the pazopanib sample size group was smaller, as well as patients were followed up for a shorter period of time compared to

sunitinib group. Yet, transition probabilities in both groups were derived by using adjusted survival curve method estimated over a 5-year period. As noted earlier, the previous study examining the CKCis database found dose individualization (dosage and/or schedule changes) to be common with the sunitinib group to allow for greater treatment adherence and reduction in the incidence of side effects.(252) However, we did not take this in consideration when estimating the cost of sunitinib, that treatment cost is likely to be reduced with alterations. A related issue is the utility value for sunitinib in the first health state, which was taken from a study where the administered regimen was the standard schedule (4 weeks on: 2 weeks off). Given the aforementioned frequent sunitinib dose individualization in patients in the CKCis database, the utility value for sunitinib used in our model may not accurately reflect current practice, but if anything, would be underestimated. Quality of life may have been greater in our cohort of patients using sunitinib compared to the clinical trials where schedule 4/2 was used, but would not be captured in our analysis. Consequently, the actual ICER/ICUR could be even lower than what was estimated by our study. This being said, we conducted a sensitivity analysis with the hypothesis of having equal utility values in pre-progression state between sunitinib and pazopanib (0.7089). In this case, the difference in QALY was 0.60 and the ICUR decreased by 8%. Other adverse events linked to the utilization of sunitinib or pazopanib such as fatigue, hypertension, nausea, could have been included in the model; however, we only included the adverse events which were statistically different between both treatments in the observational study presented above(252). In addition, our study was limited to clear cell carcinoma patients, as we did not include other histology in the survival curves. Finally, it is worthy mentioning that the unit prices included in our analysis reflect the drug list of the Quebec province, which may be different from other Canadian provinces and does not reflect any product listing agreement that may be present between the manufacturers and

provincial institutions. As these can affect both sunitinib and pazopanib prices, we cannot anticipate the impact on the ICER.

Considering the increasing number of treatment options in mRCC, this analysis can inform decision-makers on current and upcoming practices and their economic repercussions, especially concerning patients who are eligible for multiple therapies. Even if the results demonstrated a clear advantage when using sunitinib from an economic perspective, the different toxicity profiles of sunitinib and pazopanib allow for physicians to choose and tailor treatments to optimize patient response.

5.6 Conclusion

This cost-utility analysis using real-world data demonstrates the economic value of sunitinib compared to pazopanib in first-line setting for mRCC patients. When taking a 5-year time horizon, sunitinib is a cost-effective option compared to pazopanib as it yielded in an incremental 0.54 QALY for an incremental cost of $36,303. As the health care system faces restricted means, cost-effectiveness analyses using real-world data are useful in determining the optimal allocation of resources and provide a more accurate clinical and economic analysis of the use of innovative cancer therapies in routine clinical practice.

Compliance with Ethical standards: The project was approved by the Research Ethics Board of each individual participating centers and all patients provided consent for entry into CKCis.
Funding statement: Sara Nazha received a scholarship award from the Canadian Center for Applied Research in Cancer Control. Dr. Dragomir obtained salary support from the Coté-Sharp Family Foundation at the McGill University Health Center. Since June 2016, she is a Fonds de Recherche du Québec - Santé (FRQS) Junior 1 Research Scholar.
***Competing interests:** No authors have any competing interests to declare.

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5.8 Tables & Figures

Table 1: Model parameters

Parameters	Sunitinib	Pazopanib	Reference
Transition probabilities (monthly probability)			
Progression free (First-line) ⇒Death	0.021	0.038	CKCis database
Progression free (First-line) ⇒Progression (second line)	0.004	0.07	
Progression free (First-line) ⇒Progression BSC	0.091	0.143	
Progression (Second-line) ⇒Progression BSC	0.172	0.191	
Progression (Second-line) ⇒Death	0.053	0.042	
Progression BSC⇒Death	0.026	0.052	
Utilities			
Progression free (First-line)	0.6832	0.7089	(340)
Progression (Second-line)	0.6309	0.6309	(339)
Progression (BSC)	0.5509	0.5509	(339)

BSC, Best supportive care

Table 2: Adverse events included in the model

Parameters	Sunitinib	Pazopanib	Reference
Probability of AEs			
Mucositis	0.16	0.07	(252)
Hand-foot syndrome	0.12	0.03	
GERD	0.07	0.01	
Liver toxicities	0.03	0.14	
Cost of AEs (CAD$) per event			
Mucositis	2,677	2,677	(359)
Hand-foot syndrome	850	850	(359)
GERD	3,358	3,358	(359)
Hepatotoxicity	3,135	3,135	(359)
Disutility of AEs			
Mucositis	-0.169	-0.169	(360)
Hand-foot syndrome	-0.1187	-0.1187	(359)
GERD	-0.1198	-0.1198	(359)
Liver toxicities	-0.308	-0.308	(361)

AE, Adverse Events; GERD, Gastroesophageal reflux disease;

Table 3: Summary of costs included in the model ($) CAD

Parameters	Sunitinib	Pazopanib	Reference
First-line therapy (monthly)	5,304	3,854	(353)
Routine care (monthly)	770	770	(339)
Progression (one-time cost)	8,043	8,043	(358)
Second-line therapy (monthly)	4,738	5,267	(353)
Best supportive care (monthly)	960	960	(339)
End-of life care costs (one-time cost)	22,270	22,270	(358)

The monthly cost of sunitinib is pro-rated over the six-week cycle as the recommended regimen is 4 weeks on medication and 2 weeks off.

Table 4: Base-case results

	Sunitinib	Pazopanib	Incremental
Total Cost ($) CAD	107,221	70,918	36,303
Adverse events	1,574	355	1,152
Progression-free (first-line treatment)	36,887	25,176	10,230
Progression (second-line)	8,553	7,801	350
Progression (BSC)	60,207	37,586	20,114
Effectiveness			
QALY	1.54	1.00	0.54
LYG	2.79	1.58	1.21
ICUR			67,227/QALY
ICER			30,002/LYG

BSC, best supportive care; LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio.

Table 5 : One-way sensitivity analysis

Sunitinib vs. Pazopanib	Incremental cost	Incremental QALYs	ICUR	Δ ICUR from base-case ($)	Δ ICUR from base-case (%)
Base-case	36,303	0,54	67,227	0	
Cost					
Cost of BSC					
−15%	31,154	0,54	57,692	-9,534	-14%
15%	33,916	0,54	62807	-4,419	6%
Cost of pazopanib (first-line treatment)					
−15%	38,287	0,54	68,369	1,142	1%
15%	34,238	0,54	61,139	-6,087	-9%
Cost of progression					
−15%	32,540	0,54	58,107	-9,119	-13%
15%	32,533	0,54	58,094	-9,132	-13%
Cost of routine					
−15%	31,067	0,54	55,476	-11,750	-8%
15%	33,983	0,54	59,724	476	1%
Cost of sunitinib (first-line treatment)					
−15%	27,591	0,54	48,490	-10,758	-18%
15%	37,478	0,54	65,866	6,618	11%
Probability					
Pazopanib First-line ⇒BSC					
−15%	30,370	0,55	55,218	-4,030	-7%
15%	34,362	0,58	59,245	-3	0%
Pazopanib First-line ⇒Death					
−15%	31,277	0,55	57,389	-1,859	-3%
15%	33,741	0,59	57,188	-2,060	-3%
Pazopanib First-line ⇒Second-line					
−15%	32,379	0,57	56,805	-2,443	-4%
15%	32,681	0,56	57,588	-1,660	-3%
Pazopanib BSC ⇒Death					
−15%	29,574	0,47	62,261	3,013	5%
15%	35,039	0,64	54,324	-4,924	-8%
Pazopanib second-line ⇒BSC					
−15%	31,777	0,56	56,643	-2605	-4%
15%	33,130	0,57	57,617	-1631	-3%
Pazopanib second-line ⇒Death					
−15%	32,144	0,56	57,298	-1,950	-3%
15%	32,908	0,57	57,132	-2,116	-4%
Sunitinib First-line⇒AE					
−15%	32,274	0,56	56,721	-2,527	-4%
15%	32,799	0,56	57,643	-1,605	-3%

Sunitinib First-line ⇒BSC					
−15%	36,541	0,58	62,197	2,949	5%
15%	29,204	0,55	52,715	-6,533	-11%
Sunitinib First-line ⇒Death					
−15%	33,408	0,58	57,108	-2,140	-4%
15%	31,682	0,55	57,188	-2,060	-3%
Sunitinib First-line ⇒Second-line					
−15%	33,831	0,58	58,029	-1,219	-2%
15%	31,353	0,55	56,390	-2,858	-5%
Sunitinib BSC ⇒Death					
−15%	35,011	0,66	52,648	-6,600	-11%
15%	30,260	0,48	62,521	3,273	6%
Sunitinib second-line ⇒BSC					
−15%	33,069	0,56	58,529	-719	-1%
15%	32,117	0,57	56,149	-3,099	-5%
Sunitinib Second-line⇒Death					
−15%	33,133	0,58	57028	-2,220	-4%
15%	31,977	0,60	52594	-6,654	-11%
Utility					
Utility BSC					
−15%	32,536	0,50	64,684	5,436	9%
15%	32,536	0,63	51,238	-8,010	-14%
Utility Second-line					
−15%	32,536	0,55	58,308	-940	-2%
15%	32,536	0,58	56,097	-3,151	-5%
Utility of Sunitinib (first-line)					
−15%	32,536	0,51	63,177	3,929	7%
15%	32,536	0,62	52,141	-7,107	-12%
Utility of Pazopanib (first-line)					
−15%	32,536	0,60	54,227	-5,021	-8%
15%	32,536	0,53	60,476	1,228	2%
Equal utility in pre-progression state					
0.7089	32,536	0,60	54,227	-5,021	-8%
Time Horizon					
3 years	22,189	0,37	59,970	722	1%
7 years	38,012	0,67	56,734	-2,513	-4%
10 years	44,265	0,81	54,658	-4,599	-7%
BSC, best supportive care; AE, adverse event; QALY, quality-adjusted life year; ICUR, incremental cost-utility ratio.					

Figure Legends:

Figure 1: **Figure 1: Markov Model**. Markov model with 4 different states. The patient can progress to different states; Progression free (first-line treatment), progression (second-line treatment), progression (Best supportive care [BSC]) and death. The patient cannot go back to his initial state.
Figure 2: Note: The ICER calculations were based on a willingness to pay corresponding to the base-case ICER, i.e., $100,000/QALY. Figure 2 Legends: Utility BSC, utility value at progression (BSC);UtilitySunitinib, utility value at progression free (Sunitinib in first-line); pSBSC_Death, probability of transitioning from BSC to Death when treated with sunitinib in first-line; pS_BSC, probability of transitioning from progression-free (sunitinib) to progression (BSC);pPBSC_Death, probability of transitioning from BSC to Death when treated with pazopanib in first-line. E.V: expected value.

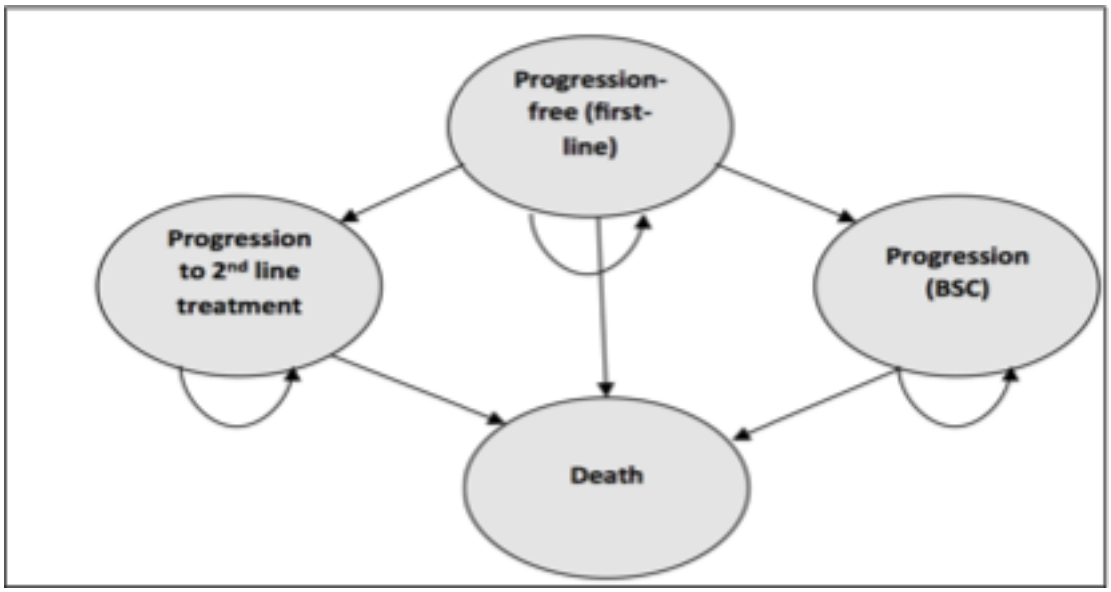


Figure 1: Markov model with 4 different states. **The patient can progress to different states; Progression free (first-line treatment), progression (second-line treatment), progression (Best supportive care [BSC]) and death. The patient cannot go back to his initial state.**

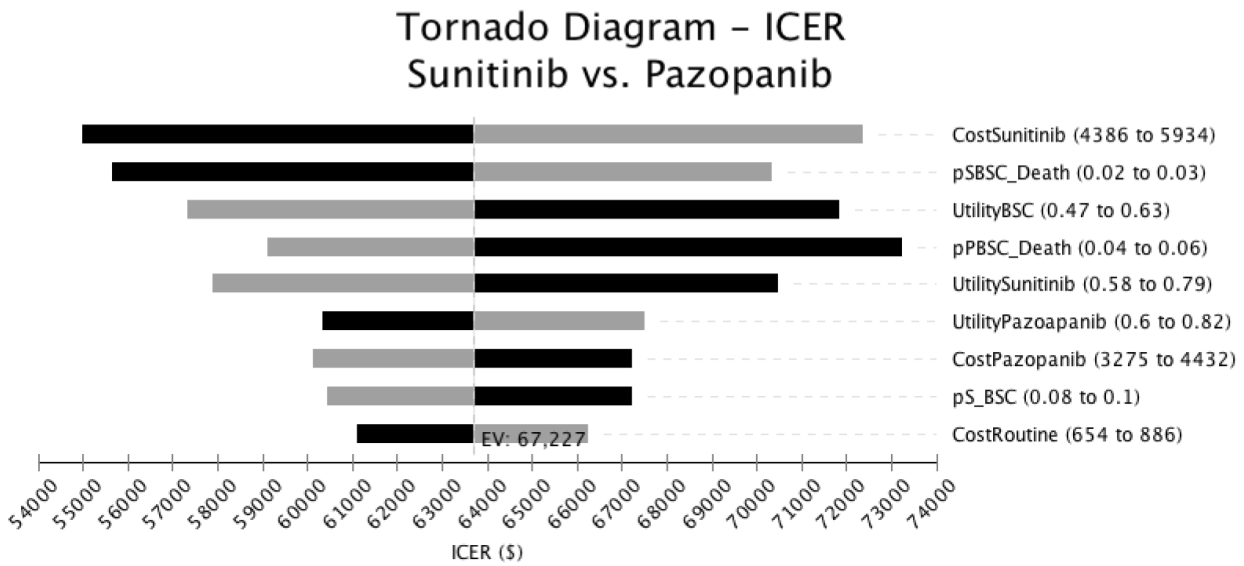
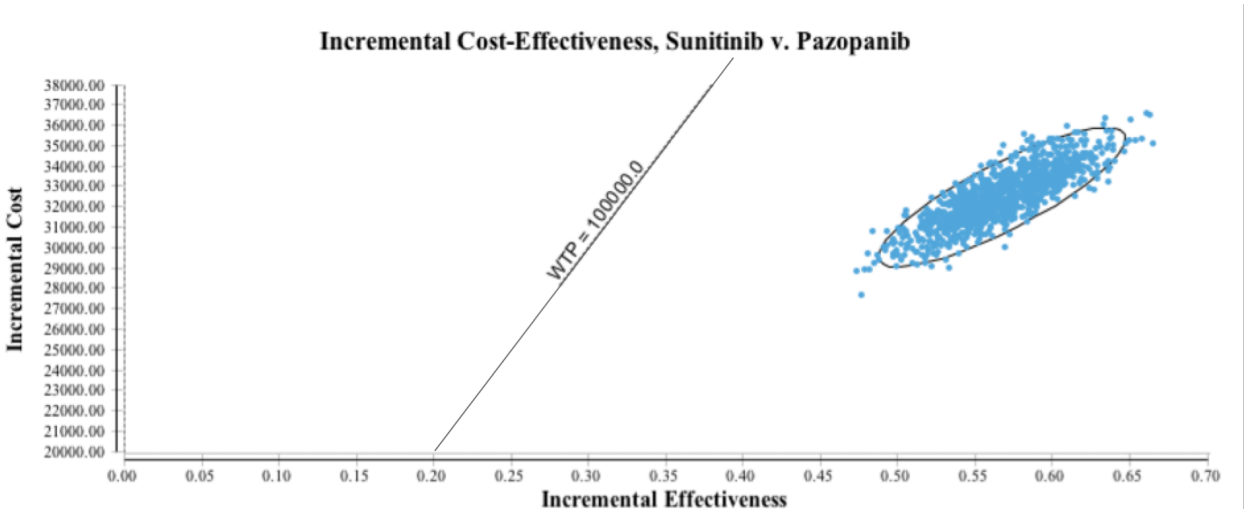


Figure 2: Tornado diagram. Tornado chart, univariate sensitivity analyses.

Note: The ICER calculations were based on a willingness to pay corresponding to the base-case ICER, i.e., $100,000/QALY.
Abbrviations: Utility BSC, utility value at progression (BSC);UtilitySunitinib, utility value at progression free (Sunitinib in first-line); pSBSC_Death, probability of transitioning from BSC to Death when treated with sunitinib in first-line; pS_BSC, probability of transitioning from progression-free (sunitinib) to progression (BSC);pPBSC_Death, probability of transitioning from BSC to Death when treated with pazopanib in first-line.E.V: expected value.



WTP : willingness-to-pay

Figure 3: Probabilistic sensitivity analysis at a willingness-to-pay threshold of $100,000.

Chapter 6: Effectiveness of metastasectomy in mRCC patients: The Canadian Kidney Cancer Information system experience.

6.1 Preface

This study presents the outcomes following surgical resection of metastasis patients with mRCC. There are no RCT in the published literature that have evaluated the beenfits related to metastasectomy. In addition, complete and incomplete metastasectomy can have different effects on patients as well as disease characteristics.

Status: Submitted to Journal of Urology

Outcomes of metastasectomy in metastatic renal cell carcinoma patients: The Canadian Kidney Cancer information system experience.

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Abstract words: 298

Text words: 2,895

Tables: 4

Figures: 2

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Keywords: KIDNEY,METASTASECTOMY, MRCC, TARGETED THERAPY.

Abstract

Background: Surgical resection of metastasis can be integrated in the management of metastatic renal cell carcinoma (mRCC) as it can contribute to delay disease progression and improve survival. **Objective:** This study assessed the impact of metastasectomy in mRCC patients using real-world pan-Canadian data. **Design, Setting and Participants:** The Canadian Kidney Cancer information system (CKCis) database was used to select patients who were diagnosed with mRCC between Jan 2011 and Apr 2019. To minimize selection bias, each patient having received a complete or incomplete metastasectomy was matched with up to 10 patients with no metastasectomy. **Outcome measurements and Statistical Analysis:** Overall survival (OS) was calculated from diagnosis of metastatic disease to death from any cause. A Cox proportional hazards model was used to assess the impact of the metastasectomy while adjusting for potential confounding variables. **Results:** A total of 417 patients had complete (273 patients) and incomplete (144 patients) metastasectomy, while 1,704 mRCC patients did not undergo a metastasectomy. At 12 months, 98.7%, 87.1% and 77.7% of patients were alive in the complete metastasectomy, incomplete metastasectomy and no metastasectomy group, respectively ($p<0.001$). After matching, patients who underwent complete metastasectomy had a longer overall survival (HR: 0.41, 95%CI:0.30-0.56) compared to patients who did not undergo metastasectomy, but this benefit was not shown in patients undergoing incomplete metastasectomy (HR: 0.95, 95%CI: 0.71-1.28) vs. non-metastasectomy patients. **Conclusion:** Our study confirmed the positive impact of complete metastasectomy performed in mRCC with an improved OS compared to patients with no metastasectomy. **Patient summary:** mRCC patients undergoing complete surgical resection of their metastasis have a longer survival than

patients undergoing an incomplete metastasectomy when compared to a group of patients who did not undergo any metastasectomy.

6.2 Introduction

Over 4000 patients are projected to be diagnosed with kidney cancer in Canada in 2017 and 1,880 will die from their disease.(366) Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers and most patients are diagnosed with clear cell histology. RCC frequently progresses to the metastatic phase, with synchronous or metachronous metastasis. In fact, over 25% of patients are diagnosed with metastasis at the initial diagnosis and 35% will later progress to the metastatic stage.(348) Since current systemic therapy does not offer complete response in most patients, surgical resection of the primary tumour and metastasis can be used to achieve long-term survival. Although metastasectomy can be successfully performed in various locations, favorable characteristics include solitary lesion, lung metastasis, curative resection at first metastasis, metachronous presentation with disease-free interval greater than 12 months, and younger age at presentation.(193, 194) Several studies have underlined the benefit of metastasectomy in mRCC patients in providing long disease free survival.(193, 196, 208) However, most studies have looked at the benefit of metastasectomy in patients who had a solitary lesion and mostly lung metastasis. In addition, these surgical procedures come with a risk of complications that are non-negligible, as previously reported in other cohort studies, where 27.5% of patients suffered major complications.(367) North American and European guidelines (138, 150, 151, 195) recommend case-by-case assessment for the need of metastasectomy, based on patient and disease characteristics. We have used the Canadian Kidney Cancer information system (CKCis), a pan-Canadian prospective registry to assess the contemporary outcome of mRCC patients who underwent metastasectomy between January 2011 and April 2019.

6.3 Methodology

Data source

Patient information and outcome data were retrieved from the CKCis database. The CKCis is a multicentre collaboration of 16 academic hospitals in 6 Canadian provinces. Clinical, demographic and pathological data for CKCis are obtained by patient survey and medical record review and includes age, sex, date of RCC and mRCC diagnosis, comorbidities, and the location and number of metastases. Complete metastasectomy was defined as surgical resection of all visible metastases present at the time of surgery, while incomplete metastasectomy was defined as resection of part of the metastases without a curative intent. Complete vs. incomplete resection was specified by patient's medical records. If the patient underwent subsequent metastasectomy at different dates, the complete vs. incomplete status was defined on the 1st metastasectomy. Research Ethics Board approval was obtained at each individual participating centres.

Study cohort

Patients diagnosed with confirmed mRCC from January 2011 to April 2019 were included in the analysis. The diagnosis of RCC was made based on histopathological evaluations of nephrectomy specimen or needle biopsy specimens in absence of nephrectomy. Index date was defined as the date of diagnosis of first metastasis confirmed by imaging. The analysis period spanned from the index date to end of follow-up, which was the earliest date between date of death, patient last visit or the end of study period (April 31st, 2019). Clinical characteristics such as age, sex, use of targeted therapy, sites of metastasis, comorbidities (hypertension, diabetes, hypercholesterolemia, cardiovascular disease, obesity and smoking), Charlson index score, time from RCC diagnosis until metastasis were identified at the index date. In order to reduce selection

bias, patients were stratified between complete and incomplete metastasectomy and then matched with up to 10 randomly selected patients among our cohort not having received a metastasectomy and having had at least an equivalent follow-up period between the index date and the date of metastasectomy or selection of non-metastasectomy patients. Variables used for the matching were age, time from RCC diagnosis until metastasis, having a nephrectomy, clear cell histology and use of targeted treatment before metastasectomy or before the date of selection of no-metastasectomy matched patients.

Statistical analysis

Clinical and demographic characteristics between complete/incomplete metastasectomy group and no-metastasectomy group were performed using Chi-squared test for categorical variables and t-test for continuous variables. Overall survival (OS) was calculated from index date (diagnosis of metastatic disease) to death from any cause. Kaplan Meier curve analysis was performed to estimate overall survival (OS) since first metastasis diagnosis in the overall unmatched cohort, with log-rank test to compare the metastasectomy group (complete or incomplete) and no-metastasectomy group. In the matched cohort, the KM curve and log-rank test were performed for the 4 groups: complete metastasectomy, incomplete metastasectomy vs. their respective matched non-metastasectomy group. The Cox proportional hazards regression model was used in matched cohort to evaluate the association between metastasectomy and survival, by adjusting for different covariables that were not used for matching, such as: sex, location of metastasis (brain, bones, lung or liver), as well as the number of sites of metastasis. An additional factor, Charlson index score, was run in a separate Cox regression model. Stratified analyses were performed in the matched cohort by use of targeted treatment prior to metastasectomy or selection, as well as by type of metastasectomy (complete vs. incomplete).

The time from mRCC diagnosis, defined as the index date, until a new metastasis was assessed for all 4 groups with a minimum of 60 days between the mRCC diagnosis and the new metastasis. All statistical tests were two-sided, with a $p < 0.05$ considered significant. All analyses were performed using the Statistical Analysis System Software (version 9; SAS Institute, Cary, North Carolina).

6.4 Results

Cohort study

Our database included 8,936 RCC patients in total, from which 2,713 had a diagnosis of metastasis. The study cohort included 2,212 patients with a 1st metastasis diagnosed between January 2011 and April 2019, with 273 patients undergoing complete metastasectomy and 144 having received an incomplete metastasectomy. The majority of patients did not undergo surgical resection of their metastasis (n= 1,704). (Figure 1)

Table 1 presents the patients demographic and clinical characteristics by groups: no-metastasectomy, incomplete metastasectomy and complete metastasectomy. In all groups, the majority of patients were male (73.5% to 79.2%). The median time between primary RCC tumour and diagnosis of metastasis was significantly longer in the complete metastasectomy group (17.4 months compared to 7.4 and 2.4 months in the incomplete resection and no metastasectomy groups respectively; p <0.001). The location of the metastasectomy was statistically different between the complete and incomplete group for locations such as lung (27.9% vs. 14.2%, p=0.0019), bone (11.7% vs. 32.6%, p=<0.001), adrenal gland (15.1% vs. 7.6%, p=0.0301) and brain (8.4% vs. 16.7%, p=0.0114).

Matched patients

As patients were matched 1 to up to 10 controls, 138 patients undergoing incomplete metastasectomy were matched with 1,120 controls that did not undergo surgery and 254 patients undergoing complete metastasectomy were matched with 1,945 controls. (Table 2) The variables used in the matching were balanced after the matching for the incomplete and complete group and their respective controls. Yet, in the complete group, histologic subtype remained statistically different as there are less non-clear cell RCC (non-ccRCC) patients eligible to be matched with non-ccRCC metastasectomy patients. Patients who underwent complete surgical resection of

metastasis had more frequent metachronous metastasis (74.1% vs. 56.5%) and a longer time between the diagnosis of primary RCC and metastasis (16.4 months vs. 7.3 months) compared to the incomplete metastasectomy group.

After matching, the median OS was not significantly different between patients undergoing incomplete metastasectomy and their matched group (49 months (95%CI 34-64) vs. 48 months (95%CI 44-53), p-value<0.971), but it was significantly different between complete metastasectomy group and their matched group (82 months (95%CI 80-NR) vs. 66 months (95%CI 60- NR), p-value=0.0001), respectively. (Figure 2) After 12 months, the proportion of patients that were still alive was 87.1% and 87.9% in the incomplete metastasectomy and its matched group. In the complete group and its respective match, the proportion of patients alive after 12 months was 98.7% and 90.5%. The proportion of patients with hypertension (50% vs. 40%) or who are smokers (4.4% vs. 0.5%), was found to be significantly greater in patients undergoing metastasectomy, whether complete or incomplete. Over 60% of patients who had a metastasectomy presented with a Charlson index score of 2 or less, whereas patients who did not undergo a metastasectomy had higher Charlson scores. The time from mRCC diagnosis until a new metastasis was assessed for all 4 groups and found to be significantly different (p<0.0001). The median time to new metastasis was 20 months (95%CI 15- 26) and 22 months (95%CI 21-27) for the incomplete metastasectomy and its matched group, respectively. The complete metastasectomy and its matched group had a median time of 40 months (95%CI 28- 47) and 30 months (95%CI 26- 32) until a diagnosis of a new metastasis, respectively (data not shown).

The multivariate regression analysis (Table 3) revealed that some locations of metastasis were associated with an increased risk of mortality such as bones (HR: 1.21, 95%CI: 0.98-1.49) and

brain (HR: 1.50, 95%CI: 1.03-2.20) metastasis, when compared to other sites of metastasis regardless of whether the patient had a metastasectomy or not. In addition, the number of sites of metastasis was associated with increased mortality (HR: 1.14, 95%CI: 1.04-1.26). Finally, having had a metastasectomy (complete or incomplete) compared to no-metastasectomy was associated with a decreased risk of mortality (HR: 0.63, 95%CI :0. 51-0.78). When including the Charlson index score in the multivariate analysis, the risk of mortality related to a metastasectomy remained similar (HR: 0.65, 95%CI: 0.52-0.81) (Table 3). Having a Charlson score of 0 to 2 versus 3 and more, was associated with a reduced risk of death (HR:0.83, 95%CI: 0.69-0.99).

Stratified analyses conducted to evaluate complete or incomplete metastasectomy vs. no-metastasectomy group are presented in Table 4. Patients that underwent complete metastasectomy had a 59% decrease risk of mortality (HR: 0.41, 95%CI:0.30-0.56) when compared to the no-metastasectomy group. In the group of patients having received targeted treatment, being candidate for a metastasectomy was still associated with a decrease in mortality when compared to not having metastasectomy (HR: 0.66, 95%CI; 0.52-0.83). In addition, a higher impact of metastasectomy was found among patients not having received targeted treatment (HR: 0.39, 95%CI: 0.23-0.67). Among patients not treated with targeted treatment, the number of sites of metastasis was associated with an increased risk of mortality (HR: 2.14, 95%CI: 1.50-3.06) but having liver metastasis was associated with a reduced risk of death (HR: 0.39, 95%CI: 0.14-0.93).

6.5 Discussion

The use of surgical resection for both primary tumor and limited metastatic disease remain an essential step to improve survival as recommended by most guidelines.(138, 150, 151, 195) Our study includes one of the largest contemporary series evaluating the effect of surgical resection of metastasis, on patient's survival, when compared to patients not treated by surgery.

COMPARISON TO OTHER STUDIES

In our cohort, nearly 13% of patients underwent complete metastasectomy, a similar proportion to that seen in other observational studies with rates of 12% to 14%.(196, 368) Complete metastasectomy were most commonly performed for lung metastasis (27.9%), given its favorable prognosis compared to other metastasis location. (196, 207) In fact, complete resection of pulmonary metastasis has been associated with a two-fold decrease in the risk of death.(369) The median age of patients at the time of metastasis is fairly consistent between studies (62-64 years-old).(196, 207) In addition, our analysis included mainly clear cell histology (79.1%), similarly to other studies (80% to 93.8%).(193, 196, 368)

After matching for potential confounders due to selection bias, the median OS of patients who had a complete metastasectomy was 82 months (95%CI: 80-NR) compared to 66 months (95%CI: 60-NR) for the matched no-metastasectomy patients. Our results are consistent with previous studies demonstrating the prolonged OS in patients undergoing complete metastasectomy compared to non-metastasectomy and incomplete metastasectomy. Many studies demonstrated similar trends as described below.

Yu *et al.* retrospectively assessed patients undergoing metastasectomy from December 2004 until

August 2013, and found a significant difference between the 3 groups with median OS of 52 months, 16 months and 22 months in the complete, incomplete and no metastasectomy group (p=0.001), respectively.(370) Another observational study including 325 patients in total reported a median OS of 92.5 months in their complete metastasectomy group, 29.6 months in the incomplete group and 23.5 months in the non-metastasectomy group (p<0.001).(368) Additionally, Alt *et al.* combined both the incomplete and non-metastasectomy patients into one group in order to compare to the complete metastasectomy group. The authors concluded that the absence of complete metastasectomy was associated with an increased risk of death from RCC (HR, 2.91; 95% CI, 2.17-3.90; p<0.001).(196)

Our stratified regression analysis demonstrated that the use of targeted therapy along with metastasectomy was beneficial for patient's survival (HR 0.66, p<0.0001). However, in patients who did not have targeted therapy, the role of metastasectomy was even more favorable (HR 0.39, p<0.0001). This likely represent a subgroup of patients with limited and more favorable metastatic disease who were rendered free of disease with surgery alone. Interestingly, we also observed an increased risk of mortality for patients having more than one organ involved with metastasis in the non-targeted treatment group. These patients who did not receive targeted treatment despite having more than one site of metastasis were probably not considered candidates for targeted treatment given their poor prognosis and advanced stage of disease. When including the Charlson index score in our multivariate analysis, we did not observe a change in the risk of death associated with a metastasectomy, as the HR was slightly impacted from 0.63 to 0.65. We can conclude that related comorbidities and the Charlson index score, did not impact the outcomes of metastasectomy after matching our population to their respective groups.

However, the use of targeted therapy in combination with metastasectomy has not been extensively reported in the published literature. In the cytokines era, some studies demonstrated moderate benefit with this combination of treatment. To our knowledge, few retrospective studies have evaluated whether metastasectomy improves the survival of mRCC patients treated with targeted therapy. In fact, Karam *et al* assessed 22 patients who had targeted treatment prior to metastasectomy. Out of the 22 patients, only one died, 105-week post-metastasectomy. The authors suggested that the approach of treating selected patients with targeted therapy prior to metastasectomy can yield in long-term tumour-free survival.(371)

LIMITATION

The main limitation of our study comes from the nature of being observational, with the main preoccupation of having a selection bias in the patient profiles, which might impact the treatment choice. While selection bias of healthier patients for surgical resection may determine observed differences in OS, we addressed this issue by performing matching analysis. In fact, our study cohort represents a heterogeneous group, with variation in the timing (metachronous or synchronous), the number of organs with metastasis, the histologic subtypes, and patient's age. Matching for these factors allowed us to balance our groups and limit the selection bias. However, some variables such as the histologic subtype was still statistically significantly different even after matching but matching on more variables would reduce significantly the sample size and statistical power.

In some cases, treatment choice might reflect patient preferences, as some patients may refuse surgical resection even if they are good candidates. It is known that the location and the number of metastasis can impact the prognosis of mRCC patients. Unfortunately, we had limited data on

the number and size of the metastasis, but we were able to adjust for comorbidities and Charlson index score, which can also impact the decision whether to undergo a metastasectomy or not. In our study we account for the location and Charlson index score, which were found independent factors associated with survival, yet we could not account for the number of tumours in each organ with metastasis or the size of the metastasis.

STRENGTHS OF THIS STUDY

One of the main strengths of our analysis, given the limited literature on mRCC metastasectomy, is the size of our cohort. In fact, our study included over 400 patients undergoing metastasectomy making it one of the largest contemporary observational study looking at metastasectomy.(198) In addition, our study includes a comparator group of non-metastasectomy patients, which is generally absent from most studies.(200)

Matching for several characteristics known to affect how patients are managed is an optimal approach to minimize selection bias. As mentioned, each patient undergoing surgical resection were matched with up to 10 patients among those who did not have a metastasectomy, for variables deemed associated with treatment choice.

6.6 Conclusion

Our study revealed that patients who underwent complete metastasectomy have a longer overall survival (HR: 0.41, 95%CI:0.30-0.56) compared to patients not receiving metastasectomy, yet a residual bias in patient selection could still be existing. These findings should support aggressive resection of metastasis in selected patients, despite that it is impossible to discriminate if the benefits observed are explained only by metastasectomy or disease intrinsic biology.

6.7 References

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6.8 Tables & Figures

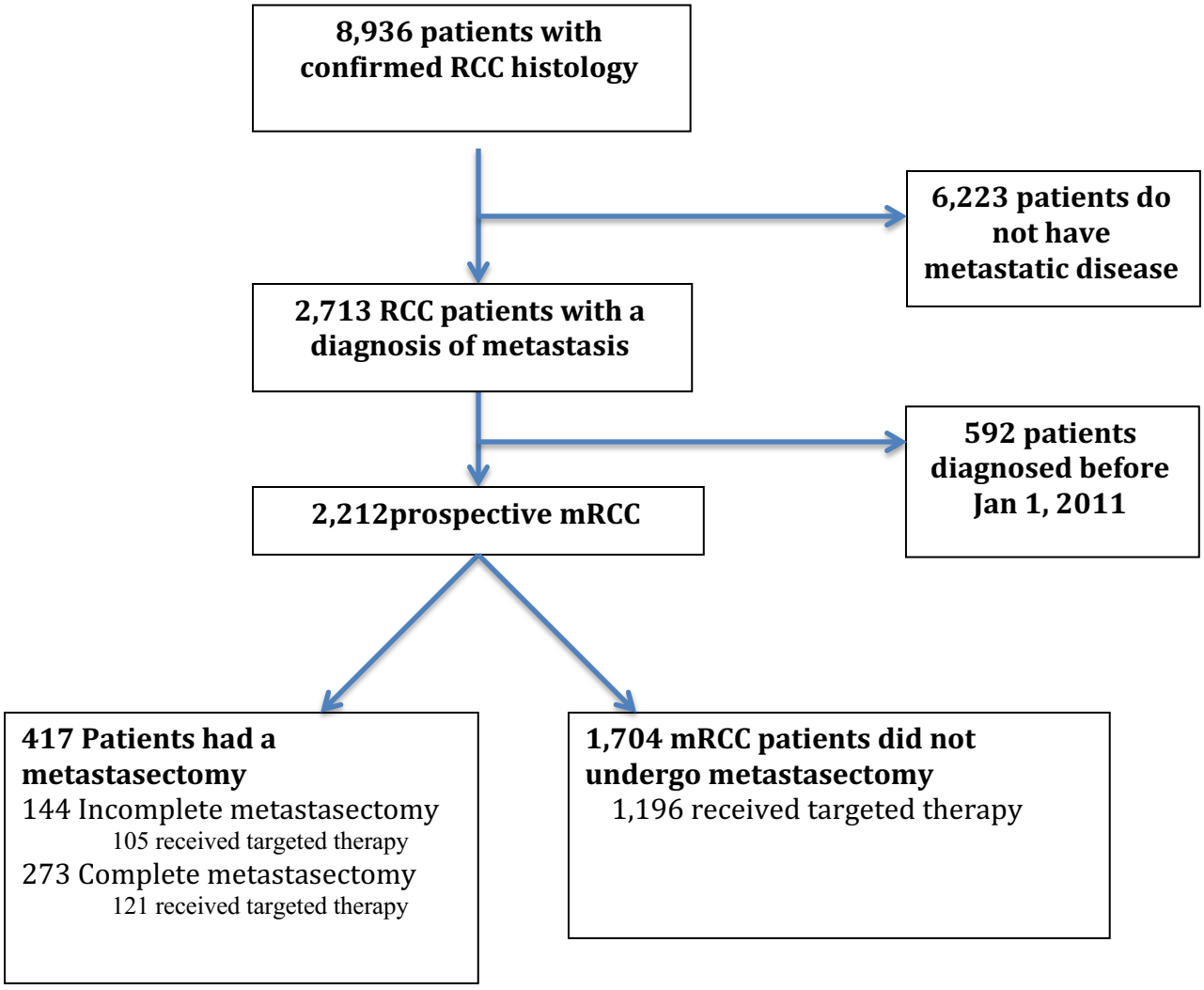

Figure 1: Flowchart Diagram

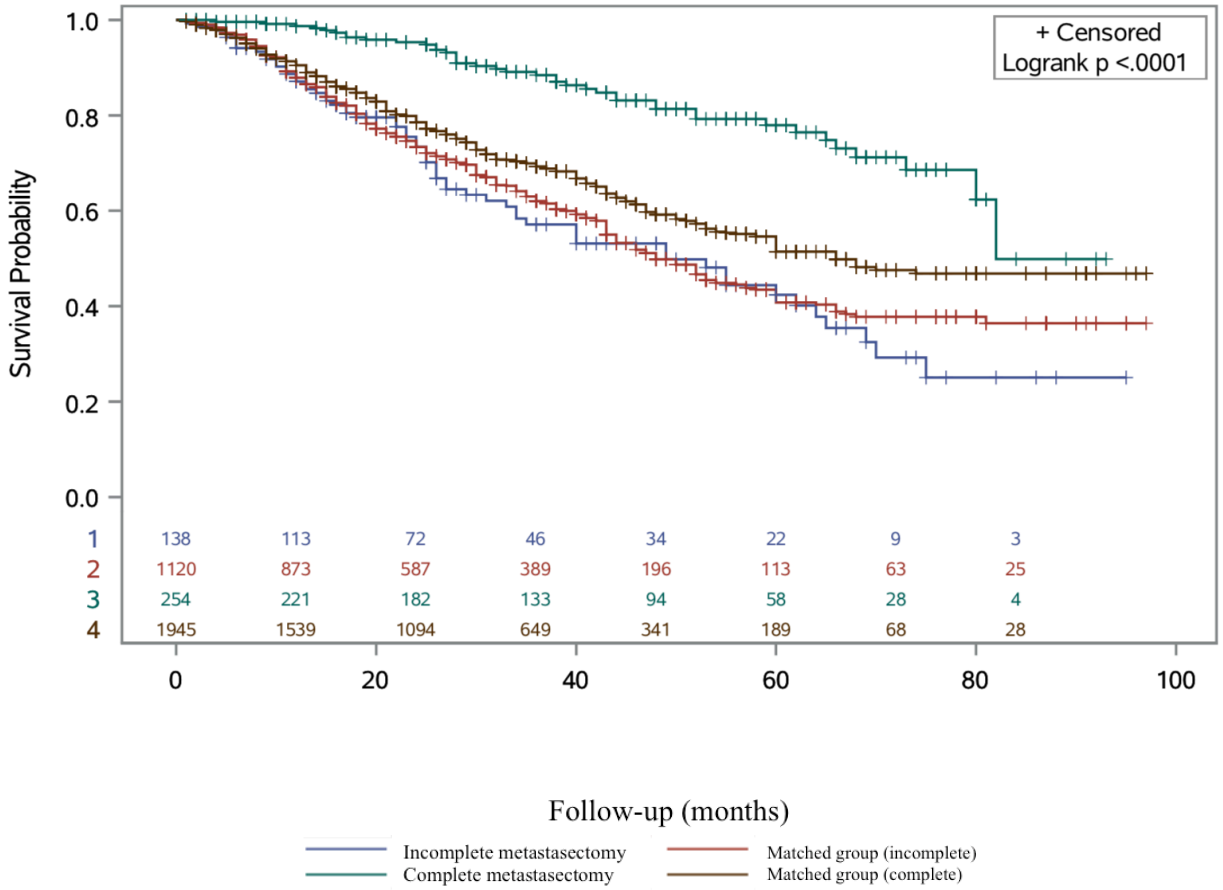

Figure 2: Kaplan Meier curve of matched groups (stratified)

Table 1: Patient characteristics (pre-matching)

	Non-Metastasectomy	**Incomplete Metastasectomy**	**Complete Metastasectomy**	***p***
No. patients	1,704	144	273	
Median Age at diagnosis (IQR)	64 (57–72)	63 (56-68)	62 (55-68)	**0.0013**
Over 65 year-old at diagnosis (%)	49.9	41.7	38.5	**0.0007**
Male	73.5	79.2	78.4	0.0923
Female	26.5	20.8	21.6	
Median follow-up (months) IQR	16 (7-33)	24 (14-47)	37 (20-58)	**0.0001***
Time between primary tumour to metastasis, median (IQR) (months)*	2.4 (0-16.6)	7.4 (0-44.8)	17.4(1-52)	**<0.001**
Over 1 year from primary tumour to metastasis (%)	28.9	41.8	52.5	**<0.001**
T stage (pathological)				
T1	19.2	22.8	25.3	0.05
T2	12.4	16.5	15	
T3	60.7	51.2	54.2	
T4	7.7	9.5	5.5	
Clear cell RCC (%)	77.9	84.7	83.9	0.0188
Synchronous metastasis (%)	49.9	43.8	24.9	**<0.0001**
Metachronous metastasis (%)	50.1	56.2	75.1	
Had a nephrectomy (%)	81.9	89.6	96.3	**<0.0001**
Location of metastasectomy (%)				
Lung	-	14.2	27.9	**0.0019**
Bone	-	32.6	11.7	**<0.001**
Adrenal	-	7.6	15.1	0.0301
Liver	-	1.4	2.2	0.5669
Brain	-	16.7	8.4	**0.0114**
Number of organs with metastasis				
1	66.7	72.9	87.8	**<0.0001**
≥2	33.3	27.1	12.1	
Metastasis location				
Lung	54.5	35.8	36.1	**<0.0001**
Bones	18.0	30.0	11.8	**<0.0001**
Adrenal	9.8	9.5	16.1	**0.0103**
Liver	10.4	7.2	3.4	**0.0009**
Brain	2.3	9.3	7.9	**<0.0001**
Targeted treatment (%)				
First-line	70.2	75.7	45.2	**<0.0001**
Second-line	28.5	31.2	24.2	0.4715
Number of metastasectomy				
1	-	81.9	82.1	0.5869
≥2	-	18.1	17.9	
Comorbidities (%)				
Hypertension	49.8	51.4	47.6	0.7243

Diabetes	20.3	25.7	16.9	0.1001
Hypercholesterolemia	19.2	22.9	19.4	0.5553
CAD	10.2	8.3	9.9	0.7685
Smoker	3.6	4.2	3.3	0.9023
Obesity	3.5	2.8	2.9	0.8067
Charlson Score Index (%)				
0	8.5	13.5	11.8	<0.0001
1	16.1	21.1	27.8	
2	24.3	35.3	24.3	
3	22.3	12.8	18.1	
4	13.6	13.5	10.9	
5	9.0	2.3	3.1	
6	6.2	1.5	2.	

*Wilcoxon test; CAD: cardiovascular disease

Table 2 : Patients characteristics (matched cohort)

	Incomplete metastasectomy	No-metastasectomy (Matched with incomplete)	*p-value* (Incomplete vs their matched no-metastasectomy)	Complete metastasectomy	No-metastasectomy (Matched with complete)	*p-value* (complete vs their matched no-metastasectomy)
No. patients	138	1,120		254	1,945	
Median Age at diagnosis (IQR)	63(56-68)	63 (55-71)	0.3754	62(55-68)	62(54-68)	0.1486
Over 65-year-old at mRCC diagnosis (%)	41.3	40.1	0.8464	38.9	41.6	0.3819
Male	78.9	75.9	0.4336	79.1	75.8	0.2386
Female	21.1	24.1		20.9	24.2	
Median follow-up (IQR)* months	24 (14-50)	24 (12-45)	0.2063	37 (19-59)	25 (14-37)	**<0.0001**
Time between primary tumour to metastasis, median (IQR)* (months)	7.3 (0-46)	3.8 (0-43)	0.6407	16.4(1-50)	10.8(0-46)	0.0778
Over 1 year from primary tumour to metastasis (%)	42.2	41.2	0.2406	51.6	49.4	0.2289
Pathological T stage at diagnosis (%)			0.5593			0.8500
T1	23.1	23.5		26.6	23.8	
T2	16.7	13.5		14.4	16.2	
T3	50.8	55.5		52.9	52.7	
T4	5.6	4.4		3.7	3.9	
Tx	3.8	3.1		2.4	3.4	
Clear cell RCC (%)	85.5	86.4	0.7663	85.4	91.2	**0.0031**
Synchronous metastasis (%)	43.5	47.7	0.3510	25.9	35.4	**0.0029**
Metachronous metastasis (%)	56.5	52.3		74.1	64.6	
Had a nephrectomy	91.3	91.9	0.7887	98.1	99.2	0.0587
Number of organ sites with metastasis						
1	71.6	72.1	0.3692	88.2	74.2	**0.0002**
≥2	28.4	27.9		11.8	25.8	
First-line targeted treatment prior to selection or metastasectomy	75.4	80.8	0.1301	44.9	48.1	0.3307
Sites of metastasis						
Lung	37.3	50.8	**0.0033**	36.3	52.3	**<0.0001**
Bones	30.6	16.5	**<0.0001**	11.8	12.1	0.9023

Adrenal	10.5	9.9	0.8456	15.1	10.9	**0.0506**
Liver	7.5	10.4	0.2879	2.9	7.8	**0.0051**
Brain	9.7	2.8	**<0.0001**	8.6	1.9	**<0.0001**
Targeted treatment (%)						
First-line	76.1	81.4	0.1325	46.3	49.5	0.3282
Second-line	31.4	33.3	0.6946	22.9	30.5	0.0861
Comorbidities						
Hypertension	52.9	40.2	**0.0042**	50.0	39.6	**0.0015**
Diabetes	26.8	16.2	**0.0018**	17.7	17.6	**0.9744**
Hypercholesterolemia	23.9	19.3	**0.1980**	20.5	18.0	**0.3367**
CAD	8.7	7.5	**0.6177**	10.6	8.4	**0.2421**
Smoker	4.4	0.5	**<0.0001**	3.5	0.7	**<0.0001**
Obesity	2.9	4.1	**0.4929**	3.2	4.8	**0.2303**
Charlson Score index (%)*						
0	14.2	8.6	**0.0031**	12.2	10.5	**0.0009**
1	19.7	21.3		27.3	19.7	
2	36.2	23.9		24.4	21.9	
3	13.4	23.4		17.2	21.3	
4	13.5	10.9		11.8	13.9	
5	1.6	6.3		3.4	6.7	
>6	1.6	5.6		3.7	6	

Table 3: Cox regression model metastasectomy (complete or incomplete) vs. no-metastasectomy.

Variables	Univariate HR	P value	Multivariate HR	P value	Multivariate HR including Charlson score	P value
Had a metastasectomy (ref : no-metastasectomy)	0.52 (0.46-0.67)	<0.0001	0.63 (0.51-0.78)	**<0.0001**	0.65 (0.52-0.81)	**<0.0001**
Male (ref: Female)	0.89 (0.78-1.02)	0.0876	0.98 (0.83-1.14)	0.7618	0.94 (0.80-1.11)	0.4666
Bones metastasis (yes vs no)	1.54 (1.31-1.80)	<0.0001	1.21 (0.98-1.49)	0.0692	1.23 (0.99-1.52)	0.0618
Liver metastasis (yes vs no)	1.38 (1.13-1.70)	0.0019	0.96 (0.74-1.26)	0.7809	1.04 (0.80-1.36)	0.7734
Lung metastasis (yes vs no)	1.13 (1.01-1.28)	0.0399	0.96 (0.81-1.13)	0.5934	0.96 (0.81-1.13)	0.5934
Brain metastasis (yes vs no)	1.27 (0.92-1.75)	0.1457	1.50 (1.03-2.20)	**0.0359**	1.61 (1.07-2.41)	**0.0215**
More than 1 location of tumour (ref: 1 location)	1.35 (1.23-1.40)	<0.0001	1.14 (1.04-1.26)	**0.0066**	1.15 (1.04-1.27)	**0.0080**
Charlson score (≤ 2 vs > 2)	0.76 (0.67-0.86)	<0.0001	-	**-**	0.83 (0.69-0.99)	**0.0362**

Table 4: Cox regression analysis by stratification groups.

Parameters	**Complete metastasectomy**	**P value**	**Incomplete metastasectomy**	**P value**	**Targeted therapy**	**P value**	**Non targeted treatment**	**P value**
N (metastasectomy vs. Non-metastasectomy)	**247 vs. 1,852**		**136 vs. 1,151**		**212 vs. 1,918**		**171 vs. 1,085**	
Had a metastasectomy	0.41 (0.30-0.56)	**<0.0001**	0.95 (0.71-1.28)	0.7254	0.66 (0.52-0.83)	**<0.0001**	0.39 (0.23-0.67)	**0.0001**
Male (ref: Female)	0.95 (0.75-1.19)	0.6244	0.91 (0.71-1.14)	0.3979	1.08 (0.91-1.29)	0.3799	0.71 (0.48-1.06)	0.0931
Bones metastasis (yes vs no)	1.57 (1.18-2.09)	**0.0022**	0.99 (0.73-1.34)	0.9562	1.28 (1.02-1.61)	**0.0342**	0.81 (0.47-1.37)	0.4243
Liver metastasis (yes vs no)	1.10 (0.76-1.58)	0.6268	0.76 (0.50-1.14)	0.1799	1.10 (0.84-1.44)	0.4874	0.39 (0.14-0.93)	**0.0364**
Lung metastasis (yes vs no)	0.99 (0.81-1.24)	0.9788	0.91 (0.71-1.17)	0.4793	1.06 (0.88-1.27)	0.5502	0.73 (0.49-1.05)	0.0904
Brain metastasis (yes vs no)	1.83 (1.08-3.10)	**0.0239**	1.17 (0.67-2.05)	0.5707	1.31 (0.85-2.03)	0.2254	2.78 (1.20-6.45)	**0.0173**
More than 1 location of tumour (ref: 1 location)	1.17 (1.01-1.35)	**0.0401**	1.18 (1.00-1.39)	**0.0274**	1.08 (0.98-1.20)	0.1260	2.14 (1.50-3.06)	**0.0003**

Chapter 7: Overall Discussion

Renal cell carcinoma is the third most prevalent urologic cancer, but accounts for the highest number of deaths in Canada between all urologic cancers (1,880 deaths in 2017).(366) The incidence of renal malignancies has increased over recent decades in the context of more widespread use of diagnostic imaging, where an increase of early stage disease is observed.(43) In fact, RCC was mainly diagnosed in its advanced stages when symptoms and signs related to this disease were observed. Given the late stage diagnosis, the prognosis of RCC was usually very low, estimating the 5-year survival in stage 4 to be less than 10%.(372) However, time trends and geographic variations in incidence and mortality may also relate to changes in the prevalence and risk factors. Many lifestyle factors such as cigarette smoking, excess body weight and uncontrolled blood pressure are the most important and modifiable risk factors for RCC.(54, 76, 373) Moreover, dietary habits associated with a Western lifestyle were proposed as potential risk factors, but no foods or food groups have been related to RCC risk.

As the management of mRCC changed since 2007 compared to the previous era, a lot of clinical research on the effectiveness of targeted therapy has been conducted globally. These research programs included many observational databases such as the CKCis and the IMDC database.(252, 254, 374) Along the effectiveness found in these observational studies, targeted therapy has replaced best supportive care or cytokine treatment as the standard of care for patients with mRCC in many countries. However, targeted therapy agents are expensive and may become a financial burden to individuals or to society.

This thesis addressed important questions in the era of pharmacotherapy for mRCC patients as

targeted treatment are the newest and most expensive treatment options for these patients. By analyzing the CKCis database, we assessed the effectiveness of sunitinib and pazopanib as first-line treatment for mRCC patients as well as the cost-effectiveness from a Canadian perspective. Finally, the role of metastasectomy for mRCC patients is not clearly stated in mRCC guidelines. Our database included one of the most prominent samples of patients undergoing complete and incomplete metastasectomy, which enables us to compare the outcome of surgical resection compared to patients who did not undergo resection of their metastasis.

7.1 Contribution to the literature

The use of pharmacotherapy in mRCC has grown with the introduction of VEGF and mTOR inhibitors. In fact, with the introduction of sunitinib and pazopanib, the standard of care has shifted as these therapies presented significant longer survival than previous treatments options. Both drugs were then compared face to face in a phase 3 RCT showing similar outcomes.(251, 375) As seen in most oncology therapies, each molecule is usually associated with its proper side-effect profiles. This being said, the availability of different molecules to treat the same cancer comes in handy for a tailored approach when treating patients in the metastatic phase and understanding the side-effect profile and utilization of these drugs. As RCT are usually conducted in restricted settings, the use of an observational database enables a comparison based on real-life practice. The CKCis database is unique as it provides an in-depth look at contemporary mRCC management in academic hospitals across Canada. This effectiveness analysis contributes to the oncologic literature by offering additional information to patients, payers and health care providers on the estimated survival of patients on first-line mRCC treatment in real-world setting.

As targeted drugs play an important role in the management of mRCC since the mid-2000s. The economic burden tagged to these therapies is substantial to the healthcare system since the average cost of therapy is estimated between $4,000 to $5,000, on a monthly basis.

The real-world utilization and effectiveness of sunitinib and pazopanib have been noted in several studies.(252, 254) Assessing the cost-effectiveness of sunitinib vs. pazopanib in mRCC patients considering real-world effectiveness has not been published previously. This real-world cost-effectiveness allows for better interpretation of the economic value of sunitinib and pazopanib and provided a benchmark to future treatment, which will be compared to these standards of care from an economic perspective. In fact, with the ongoing phase 3 studies looking into immunotherapy combinations such as ipilimumab+nivolumab, the ICER of this combo compared to sunitinib will be assessed to develop reimbursement recommendations. The use of an economic value based on real-world data can benefit the decision–makers for accurate analysis.

Also, as mRCC patients can be presented with resectable disease, the use of surgical resection for primary tumour and metastasis location is often used to manage patients and even cure them. The published literature does not present any RCT comparing the use or not of metastasectomy in mRCC patients. This being said, the proven efficacy and the studies supporting guidelines recommendations are all based on observational databases. Our study, being one of the biggest in sample size, provides additional information on the role of metastasectomy in mRCC patients as well as further understanding on the patient's disease-related characteristics that are linked with better prognosis.

7.2 Summary of major findings

Study 1

The purpose of this study was to assess the effectiveness and cost of targeted therapies for patients with clear cell mRCC treated with sunitinib or pazopanib in first-line setting using the CKCis database.

This analysis included 475 mRCC patients treated with targeted treatments. Most patients (81%) were treated with sunitinib in first-line and 19% were treated with pazopanib. The median TTT in first-line for sunitinib and pazopanib patients was 7.7 and 4.6 months, respectively (p<0.001). A statistically significant difference of 11 months was seen between the overall survival of sunitinib and pazopanib in first-line (32 vs. 21 months, respectively). The main factor that can explain this difference is dose scheduling in patients treated with sunitinib. When a conditional survival analysis was used to estimate the median overall survival of patients one year post-treatment initiation, the difference between both treatments was even greater than the difference in overall survival since the initiation of first-line therapy. The choice of therapy was the only factor associated with risk of death when analyzing conditional survival at 1-year. Consequently, it seems that beyond 12 months of therapy, the predictive value of baseline characteristics for mortality is reduced.

The cost of treating patients with targeted therapy is substantial as the median cost of up to 2 lines of therapy was $56, 476 (IQR: $23,738 - $130,447) for the sunitinib group, which is $10,224 higher than the pazopanib group. When the cost of treatment is adjusted for the survival of patients, the cost of treatment when initiated with sunitinib per month becomes lower than for pazopanib, as patients tend to live longer: $1,765/month vs. $2,202/month in the sunitinib and pazopanib group, respectively.

This analysis confirms the efficacy of pazopanib and sunitinib in first-line setting using real-world data, with better overall survival observed in the sunitinib group linked to a different practice and dosage scheduling.

Study 2

The objective of the second study was to estimate the cost-utility of sunitinib vs. pazopanib in Canada based on real-life utilization, which should be the closest illustration of real-life practice and the most accurate estimation of the costs engendered.

The ICUR found in our analysis was $67,227/QALY and the ICER was $30,002/LYG. These ratios are acceptable given the standard thresholds to be around $50,000-$100,000/QALY in the field of oncology. The difference in cost found between sunitinib and pazopanib in first-line setting is mainly driven by the longer time to treatment failure in patients using sunitinib in first-line. When looking at the OS (33.51 months) for sunitinib, we realized that patients reside a significant time in the BSC state, which explains its high sensitivity in the deterministic sensitivity analysis.

This cost-utility analysis using real-world data demonstrates the economic value of sunitinib compared to pazopanib in first-line setting for mRCC patients. When taking a 5-year time horizon, sunitinib is a cost-effective option compared to pazopanib as it yielded an incremental 0.54 QALY for an incremental cost of $36,303.

As the health care system faces restricted means, cost-effectiveness analyses using real-world data are useful in determining the optimal allocation of resources and provide a more accurate clinical and economic analysis of the use of innovative cancer therapies in routine clinical practice.

Study 3

With the availability of a pan-Canadian database, we assessed the outcome of metastasectomy in mRCC patients using real-world data from Canadian academic centers from January 2011 until April 2019.

Our database included 8,936 RCC patients in total, from which 2,713 had a diagnosis of metastasis. The study included 2,713 patients in total with 273 patients undergoing complete metastasectomy and 144 having received an incomplete metastasectomy. The majority of patients did not undergo surgical reception of their metastasis (n= 1,704).

At 12 months from index date, most patients in the complete and incomplete metastasectomy group were still alive (99.1.5% and 88%, respectively). At 12 months, 98.7%, 87.1% and 77.7% of patients were alive in the complete metastasectomy, incomplete metastasectomy and no metastasectomy group, respectively ($p<0.001$). After matching, patients who underwent complete metastasectomy had a longer overall survival (HR: 0.41, 95%CI:0.30-0.56) compared to patients who did not undergo metastasectomy, but this benefit was not shown in patients undergoing incomplete metastasectomy (HR: 0.95, 95%CI: 0.71-1.28) vs. non-metastasectomy patients.
After matching, the median OS was not significantly different between patients undergoing incomplete metastasectomy and their matched group (49 months (95%CI 34-64) vs. 48 months (95%CI 44-53), p-value<0.971), but it was significantly different between complete metastasectomy group and their matched group (82 months (95%CI 80-NR) vs. 66 months (95%CI 60-NR), p-value=0.0001), respectively

Even though cure is not possible, improved survival can be achieved with combination therapy

using metastasectomy. Younger patients, with limited number of metastases and favorable locations such as lungs should be considered for surgical resection of metastases.

7.3 Overall limitations and strenghs

Strengths

Strengths of our analysis include the large multicenter database that focuses on patients managed for kidney cancer across several Canadian academic hospitals. In fact, the CKCis database includes over 8,000 patients with a diagnosis of kidney cancer from January 2011 until present. The Canadian Kidney Cancer information system (CKCis) is a multicentre collaboration of 16 academic hospitals in 6 Canadian provinces (McGill University Health Center, Capital Health Queen Elizabeth II Health Sciences Centre, SMBD Jewish General Hospital, Centre Hospitalier de l'Université de Montréal (CHUM), Centre Hospitalier Universitaire de Québec (CHUQ), Ottawa Hospital, University Health Network, Sunnybrook Health Sciences Centre, Hamilton Health Sciences St. Joseph's Hospital & Juravinski Cancer Centre, London Health Sciences Centre & St. Joseph's Healthcare, Cancer Care Manitoba, Tom Baker Cancer Centre, Southern Alberta Institute of Urology, Cross Cancer Centre, University of Alberta Health Centre and Vancouver General Hospital). Unlike clinical trials, CKCis includes mRCC patients treated in real-life clinical practice, strengthening its use as a population-based method of analysis. (Appendix 1)

One the main advantages of having an observational database is the opportunity to describe how patients are treated and the following outcomes based on real clinical practice. In fact, this allows for a better understanding of the patient or disease-related characteristics linked with specific treatment patterns. As all targeted treatments are evaluated in RCTs, the CKCis database is of great value to compare the outcomes of mRCC patients who are treated outside of RCTs. In fact, this benefit allowed us to understand the way patients are treated with targeted therapy such as sunitinib. Observing a statistically significant difference in overall survival due to how patients were

receiving therapy allows a more accurate prediction of patient survival and may equip health care professionals with additional information on patients' prognostic which can be useful in clinical practice.

Given the large number of patients found in the database, our studies were capable of comparing a significant number of patients in the different treatment groups. In fact, the number of patients found in our dataset treated with metastasectomy is one of the biggest analyses in the field of mRCC metastasectomy to date. This strength was useful in our third objective. In fact, our study included over 300 patients undergoing metastasectomy making it one of the biggest observational studies looking at metastasectomy along with Naito *et al.* which included 125 patients undergoing surgical resection in their analysis.(198)

Limitations

Given the observational nature of our database, conducting studies with a comparative objective leads to selection bias. This limitation is found by default in all observational analyses; however; many solutions can be applied to limit the selection bias. As a matter of fact, matching cohorts and multivariate analyses, as well as survival curve adjustment, are all methods used in our analyses to account for the differences seen between the patient groups. Some specific limitation observed in our analysis due to the observational nature of our studies were the unbalanced proportion of patients between different groups evaluated, such as the first-line treatment groups between sunitinib and pazopanib or the proportion of patients having a complete vs. incomplete metastasectomy. Furthermore, the adjustment of dosage and treatment scheduling was not optimally reported in the database, which limits the generalizability of our analysis, especially in patients treated with sunitinib. A related issue is the utility value for sunitinib in the first health

state, which was taken from a study where the administered regimen was the standard schedule (4 weeks on: 2 weeks off). Given the frequent sunitinib dose individualization in patients in the CKCis database, the utility value for sunitinib used in our model may not accurately reflect current practice, but if anything, would be underestimated.

Our studies only include academic centres, which can be seen as a selection bias since treatment patterns and patient characteristics may be different from the community setting. In order to enable comparison with randomized controlled studies, only patients with clear cell histology were included in our study; however, it is known that targeted treatments are used in non-clear cell mRCC patients in real-life, which is not reflected in our study. Finally, in some cases, treatment choice might reflect patient preferences, as some patients may refuse surgical resection or targeted treatment even if they are good candidates. This underlying bias is a standard limitation that limits the external validity of observational studies in general.

7.4 Implications for access to care for patients and health service delivery.

In the current landscape, patient access to healthcare, more precisely pharmacotherapy, is managed by many processes throughout different bodies such as physicians, hospital formulary decision, private payers, public payers and health technology assessments bodies. Given the societal perspective in Canada, the general population is part of the process too and is even directly linked to health technology assessments by being able to provide input when therapies are under review.

The current model in Canada and many other countries rely on expenditure caps and global budget as mechanisms to contain costs of the healthcare budget. Global budgets can be unilaterally set by payers or negotiated between payers and providers. As a matter of fact, the cost of therapies set by pharmaceutical manufacturers plays an important role in the access for patients. In fact, a price that

is seen as excessive by decision makers will usually require additional negotiations and analyses in order to have an agreement from both parts.

Since many health technology assessments underline the need for real-world evidence, criteria for reimbursement are usually restricted in order to control the use of these drugs, which are still subject to uncertainty. The value of our study falls right into the need of payers as observational analyses answer direct questions about the use of drugs outside of RCT, which are the main form of studies submitted for reimbursement assessment. In fact, the CKCis database has already been used in CADTH submission for the re-evaluation of targeted therapy such as axitinib, in the second line for mRCC patients in Canada. The submission of additional data outside of RCT led to a positive recommendation in the use of axitinib in second-line.(376)

In addition to the economic impact, our research projects are valuable for patient and healthcare delivery as many evidence have been developped on prognostic and response rates.

7.5 Future research

Finally, since pharmacotherapy in mRCC is expanding as well as its costs, additional studies covering the whole disease spectrum in the real-life setting should be conducted to optimize mRCC management. Also, as new therapies are under development and showing higher response rates compared to current targeted therapies, such as atezolizumab, combination therapies such as pembrolizumab+axitinib and the ipilimumab+nivolumab combination, further studies should be conducted on the sequential use of systemic treatment and surgical resection for optimal management of mRCC patients with good performance status. Future studies looking into the cost-effectiveness of metastasectomy could be conducted too in order to better assess the value of such surgical management in the spectrum of the disease.

Overall, there is an opportunity to develop comprehensive economic model that will allow to model the whole disease spectrum from early diagnosis of small renal masses to more advanced stages as metastatic disease. Finally, for better estimation of the economic and clinical burden of RCC in its totality, a review of the global management of the disease and its related costs should be conducted as a benchmark for future cost-effectiveness studies or cost-of-illness analysis.

In addition, meaningful work has been conducted on the genetic basis of RCC. There is significant need to assess the cost-effectiveness of genetic tools in early RCC in order to evaluate the economic impact of stratifying RCC patients by risk and to demonstrate the potential savings from the Canadian Health care system perspective. By demonstrating the cost-effectiveness of interventions, we will assist the decision-making process, which would ultimately lead to the best therapeutic options being offered to individuals patients, improve overall patient care, and reduce health care expenditure.

7.6 Conclusion

Novel health interventions might improve health outcomes, but it is associated with an economic burden which government and decision-makers take highly into consideration. In addition, these novel therapies are usually related to incremental effectiveness in specific sub-population. The availability of real-world data comes in handy as a source of reliable information to understand the actual clinical and economic burden of a disease and its related management costs.

In this thesis, comparative costs and QALYs of targeted therapies for mRCC have been evaluated over the lifetime of patients from diagnosis to end-of-life with the conclusion that costs and outcomes of management strategies vary substantially. Assessment of costs and QALYs associated with management strategies helps to decide upon the best management option and prevent the

health care budget from being overspent. In addition, the use of metastasectomy to improve the outcomes of mRCC patients was assessed, which is valuable information benefiting physicians and their patients in understanding the place of each therapy in the management of mRCC.

Finally, real-world data can provide valuable information for decision-maker such as regulatory and reimbursement bodies. In fact, in the past year, we have seen significant use of real-world evidence from regulatory bodies such as the FDA to approve new drugs such as palbociclib in men's breast cancer as well as avelumab in merkel cell carcinoma. These significant milestones are concrete examples of the future use of real-world evidence and it's considerable impact.

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