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Outcome of patients with metastatic, papillary renal cell carcinoma: 10- year single centre experience

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Zusammenfassung:

Hintergrund:
Gezielte Therapien wie VEGF-, mTOR-Inhibitoren und Immun-Checkpoint-Inhibitoren (ICIs) sind etablierte Behandlungsstrategien beim metastasierten klarzelligen Nierenzellkarzinom (NCC), beim papillären RCC (papNCC) fehlen jedoch Beweise der Stufe 1. Die Beweise stammen aus einarmigen Studien, erweiterten Zugangsplänen und Subguppenanalysen größerer NCC-Studien. Der derzeit wirksamste Behandlungsansatz für Patienten mit papNCC stellt einen ungedeckten therapeutischen Bedarf dar.

Ziel der Arbeit:
Ziel dieser Dissertation war es, die Ergebnisse von Patienten mit metastasiertem papNCC zu analysieren, die zwischen 2005 und 2015 in der Klinik für Urologie des Universitätsklinikums München Großhadern der Ludwig-Maximilians-Universität behandelt wurden. Unser Ziel war es, die Wirksamkeit verschiedener systemischer Therapien zu vergleichen und Ergebnisse wie Therapieansprechen, progressionsfreies Überleben (PFS) und Gesamtüberleben (OS) zu beschreiben. Wir haben auch klinische und pathologische Ausgangsmerkmale analysiert, die sich auf die Patientenergebnisse auswirken können. Darüber hinaus wollten wir die relevante Literatur überprüfen und die onkologischen Ergebnisse verschiedener systemischer Therapien bei Patienten mit metastasiertem papNCC vergleichen, um diese Arbeit in einen relevanten Kontext zu stellen.

Ergebnisse:
Hierbei handelt es sich um ein retrospektives Audit an einem einzigen Zentrum, bei dem Daten über einen Zeitraum von 10 Jahren gesammelt werden. Die mittlere Nachbeobachtungszeit für diese Patientengruppe betrug 71 Monate (95 %-KI: 24–118), was die Längste in der aktuellen Literatur berichtete Dauer darstellt. Die Ausgangscharakteristika von Patienten und Tumoren ähneln denen, die zuvor in der Literatur beschrieben wurden. Das mittlere krankheitsfreie Überleben (DFS) nach der Operation betrug 14,9 Monate (95 %-KI: 2,5 – 27,3) und 43 % der Patienten entwickelten nach der ersten Operation mit kurativer Absicht eine Metastasierung. Es gab keinen statistischen Unterschied im OS bei Patienten, die sich einer cytoreductive Nephrektomie unterzogen im Vergleich zu denen, bei denen dies nicht der Fall war (9,8 vs. 7,7 Monate, p = 0,777). Alle Patienten erhielten eine Erstlinientherapie, jedoch erhielten nur 48 % eine Zweitlinientherapie, 21 % eine Drittlinientherapie und 5 % eine Viertlinientherapie. Das mittlere OS betrug 10,5 Monate (95 %-KI: 5,4 – 15,7). Der Prozentsatz der Patienten, die nach 1 Jahr, 2 Jahren und 5 Jahren noch am Leben waren, betrug 41 %, 31 % bzw. 5 %. Sunitinib war bei 74 % der Patienten das am häufigsten eingesetzte Erstlinientherapeutikum. Die Gesamtansprechrate bei diesen Patienten betrug 26 %, wobei 10 % eine vollständige Remission erreichten. Basierend auf den Ergebnissen der aktuellen PAPMET-Studie (NCT02761057) ist Cabozantinib aufgrund der höheren Ansprechrate (23 % vs. 4 %) und des günstigeren PFS (HR 0,60 [0,37–0,97], p = 0,019) im Vergleich zu Sunitinib. Die Kombination von ICI- und VEGF-Inhibitoren hat die Therapielandschaft des klarzelligen NCC verändert, und es ist wahrscheinlich, dass diese Wirkstoffe auch beim papNCC eingesetzt werden. Zu den Einschränkungen dieser Arbeit gehören der retrospektive Charakter der Datenerhebung und die geringe Anzahl von Patienten. Darüber hinaus gab es keine mit Cabozantinib behandelten Patienten, da diese Therapieoption zu diesem Zeitpunkt nicht zugelassen war. Das relativ lange Überleben einiger Patienten ist auf den starken Selektionsbias zurückzuführen.

Schlussfolgerungen:
Diese retrospektive Single-Center-Kohortenanalyse zeigte, dass VEGF-Inhibitoren wirksam sind und im Vergleich zu mTOR-Inhibitoren bessere Ergebnisse hinsichtlich Ansprechrate und

Überleben erzielen. Zusammen mit der fundierten Zusammenfassung der derzeit verfügbaren Daten trägt diese Arbeit zur Etablierung einer evidenzbasierten Therapie des metastasierten papNCC bei.

Abstract:

Background:
Targeted therapies such as VEGF-, mTOR- inhibitors and immune checkpoint inhibitors (ICIs) are established treatment strategies in metastatic clear cell renal cell carcinoma (RCC), however level 1 evidence is lacking in papillary RCC (papRCC). Evidence is derived from single-arm trials, expanded access schemes and subgroup analysis of larger RCC studies. Currently the most effective treatment approach for patients with papRCC represents an unmet therapeutic need.

Objective:
The aim of this dissertation was to analyse the outcome of patients with metastatic, papRCC who received treatment between 2005 – 2015, in the Department of Urology, University Hospital Munich Grosshadern, Ludwig-Maximilians University. We aimed to compare the effectiveness of different systemic therapies used and describe outcomes such as response to therapy, progression free survival (PFS), and overall survival (OS). We also analysed baseline clinical and pathological features which may influence patient outcomes. Furthermore, we aimed to review the relevant literature comparing the oncological outcomes of different systemic therapies in patients with metastatic papRCC in order to put this research into relevant context.

Results and limitations:
This is a retrospective, single centre audit with data collected over a period of 10 years. The median follow-up for this patient population was 71 months (95%CI, 24-118) which is the longest reported in the current literature. Baseline patient and tumour characteristics are similar to those previously described in the literature. The median disease-free survival (DFS) post-surgery was 14.9 months (95% CI, 2.5 – 27.3) and 43% of patients developed metastatic disease after initial surgery with curative intent. There was no statistical difference in OS in patients undergoing cytoreductive nephrectomy compared to those who didn't (9.8 vs 7.7 months, p=0.777). All patients received front-line therapy, however only 48% received second line, 21% received third line and 5% received fourth line, subsequent therapies. The median OS was 10.5 months (95%CI, 5.4 – 15.7). The percentage of patients who were alive at 1 year, 2 years and 5 years were 41%, 31% and 5%, respectively. Sunitinib was the most frequently used first line therapy agent in 74% of patients. The overall response rate in these patients was 26% with 10% achieving complete response. Based on the results of the recent PAPMET trial (NCT02761057), cabozantinib is currently the recommended front-line therapy agent due to higher response rate (23% vs. 4%) and more favourable PFS (HR 0.60 [0.37–0.97], p = 0.019) compared to sunitinib. The combination of ICI and VEGF inhibitors have changed the therapy landscape of clear cell RCC, and it is likely that these agents will be adopted in papRCC as well. Limitations of this work include the retrospective nature of the data collection, and small number of patients. Furthermore, there were no cabozantinib treated patients as this therapy option was not approved at the time. The relatively long survival in some of the patients is attributed to the heavy selection bias.

Conclusions:
This retrospective, single centre cohort analysis showed that VEGF-inhibitors are effective and have superior outcomes with regards to response rate and survival when compared to mTOR inhibitors. Together with the robust summary of currently available data, this work contributes towards the establishment of evidence-based therapy of metastatic papRCC.

1. INTRODUCTION

1.1. Epidemiology

Renal-cell carcinoma (RCC) is worldwide the 16th most frequent cancer with approximately 431.000 new cases diagnosed each year which represents 2.2% of all new cancer cases [1]. The mortality rates of RCC have steadily declined over the last two decades and reached approximately 180.000 patients in 2020 [1]. This decline is due to earlier and often incidental diagnosis of RCC by standard imaging like ultrasound or cross-sectional imaging with computed tomography. Between 2004 and 2010 the percentage of stage I RCC raised from 50% to 58%, whereas stage IV cases decreased from 18% to 15% [2].

1.2. Etiology

Age and gender are strongly associated with the risk of developing RCC. It occurs almost twice as often in male as in female patients [3]. The cumulative risk of developing RCC (ages 0-74) is 0.51% with the highest rates in those over 85 years [3]. Several clinical/lifestyle factors have been identified as contributing factors for developing RCC. These include smoking, obesity, hypertension, antihypertensive medication, and end-stage renal disease.

- Smoking

Tobacco smoking is clearly associated with the development of RCC as shown in the VITAL study [>37.5 pack-years vs never: HR 1.58, (95% CI 1.09–2.29)] [4] with a pronounced, dose-dependent rise in risk correlated with the quantity of cigarettes smoked daily and a significant decrease in risk for patients who quit smoking [5,6].

- Obesity

Increased body-mass index (BMI) is associated with the development of several cancer types, including RCC. A study conducted by Macleod et al. confirmed that obesity is significantly associated with the development of RCC [BMI ≥35 vs <25 kg/m^2: HR 1.71, (95% CI 1.06–2.79)] [4]. The relative risk corresponding to 5 kg weight increases the risk of RCC by 25% in men and 35% in women [7].

- Hypertension

Several prospective cohort-studies have shown that patients with high blood pressure treated with antihypertensive medication are more likely to develop RCC [8,9]. In the VITAL study, hypertension was linked with a 70% increase in risk for developing RCC [HR 1.70, (95% CI 1.30–2.22)] [4]. The biological mechanisms remain unclear, but it has been postulated that patients with hypertension may also experience chronic renal hypoxia leading to the transcription of hypoxia-inducible factors. These in turn that boost tumour cell proliferation and angiogenesis [10].

- Chronic kidney disease

Patients with end-stage renal disease (ESRD) with acquired cystic kidney disease are at least 10 times likelier to develop RCC than the general population [11] with an overall incidence of 4% [12]. Furthermore, papillary RCC is more prevalent in patients with ESRD (21.9% vs. 9.7%) [13,14].

1.3. Histopathological classification of renal tumours

In 2004 the WHO defined a comprehensive histological classification system for renal neoplasms [15] which was modified and extended in 2013 by the International Society of Urological Pathology [16]. Today we use the 2022 World Health Organization classification of tumours of the urinary system and male genital organs (5th edition) to characterise all renal neoplasms [17]. It combines the traditional morphology- based classification system with the results of molecular diagnostics introducing the new term of molecular-driven renal tumours [17].

The histological subtypes of renal neoplasms defined according to the novel WHO classification is shown in **Table 1** and their morphological characteristics, and molecular alterations in **Table 2.**

Table 1 – Renal tumours according to the 2022 WHO classification [17]

Renal cell tumours	**Clear cell renal tumours** **Papillary renal tumours** **Oncocytic and chromophobe renal tumours** **Collecting duct tumours** **Other renal tumours** **Molecularly defined renal carcinomas**
Metanephric tumours	
Mixed epithelial and stromal renal tumours	
Renal mesenchymal tumours	Adult renal mesenchymal tumours Paediatric renal mesenchymal tumours
Embryonal neoplasms of the kidney	Nephroblastic tumours
Miscellaneous renal tumours	Germ cell tumours of the kidney

RCC arises from the nephrons with different histologic subtypes originating from different cells. Clear-cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (papRCC) originate from the proximal tubule, whereas chromophobe RCC and oncocytoma stem from the distal tubule [18,19]. The collecting duct and medullary renal cell carcinoma originate from the Bellini's ducts and the renal medulla, respectively[20]. The most common subgroups of RCC are described in more detail below.

1.3.1. Clear cell renal cell carcinoma (ccRCC)

Clear-cell RCC is the most prevalent histologic subtype, representing more than 75% of all renal tumours. The cells present clear or eosinophilic cytoplasm within a delicate thin-walled blood vessel vascular network. Typically, they exhibit a well-defined membrane or pseudocapsule and often display features such as cysts, necrosis, haemorrhage, and calcification. The most frequently observed growth patterns are alveolar and acinar. Mutations leading to the development of sporadic and hereditary clear-cell RCC occur within the von Hippel-Lindau (VHL) gene. It is an autosomal dominant tumour suppressor, located on the short arm of chromosome 3 [21].

1.3.2. Papillary renal cell carcinoma (papRCC)

Papillary renal cell carcinoma is the second most prevalent histologic subtype, making up roughly 13-20% of all cases of RCC. Both types possess unique clinico- pathologic and molecular profiles and can occur sporadically or as part of an inherited syndrome. The tumour displays a papillary or tubulo-papillary architectural pattern, often accompanied by calcifications, necrosis, and the presence of foamy macrophages as common histological characteristics. It used to be further divided into two groups: type 1 and 2 papRCC as proposed by Delahunt and Eble in 1997 [22], however as of the newest edition of WHO classification, no longer recommends this. Papillary RCC exhibits significant molecular heterogeneity, ranging from low to high grade tumours[23]. Frequently, these tumours exhibit chromosomal gains in chromosomes 7 and 17, accompanied by the loss of chromosome Y. Low-grade papillary RCC commonly features alterations in the MET gene. In contrast, high-grade papillary RCC may display aberrations in genes related to the CDKN2A, MYC pathway, as well as the NRF2/ARE pathway [24,25]. Recent translational studies suggest that papRCC is made up of multiple molecular subgroups [25]. The definition of papRCC is constantly evolving, and some subgroups are now regarded as independent tumours with specific clinical and molecular background, for example, sporadic FH-deficient RCC, tubulocystic RCC, ESC RCC, clear cell papRCC, SMARCB1-deficient RCC, and MiTF family RCC.

1.3.3. Chromophobe renal cell carcinoma (chRCC)

Chromophobe renal cell carcinoma, which is the third most prevalent subtype of RCC, was initially characterized in the mid-1980s by Theones et al and accounts for 5-7% of RCCs [20]. Microscopically, chRCC cells are large, unencapsulated with a voluminous cytoplasm. Chromophobe tumours generally have a better prognosis when compared to ccRCC and papRCC [26]. Genetically chRCC is distinguished by significant chromosomal loss, most often 1, 2, 6, 10, 13, and 17. Most chRCC are sporadic, however it can occur as part of a genetic syndrome named Birt-Hogg-Dubé. This is an autosomal dominant disorder where patients generally present with bilateral and multifocal RCC and numerous pulmonary cysts which can result in spontaneous pneumothorax.

1.3.4. Oncocytoma

Oncocytoma is a benign neoplasm accounting for 6–9% of all renal tumours [27]. Microscopically, they are well-circumcised tumours with no tumour capsule. The cells of oncocytomas typically exhibit a polygonal shape, abundant eosinophilic cytoplasm, and uniform, round nuclei. Most oncocytomas slowly grow in size with an annual growth rate of approximately 10 mm [28].

1.3.5. Carcinoma of the collecting duct of Bellini

Collecting duct carcinomas are rare renal neoplasms (<1%) which originates from the distal collecting duct and characterised by infiltrating glands growing in a tubulo- papillary pattern with a desmoplastic stroma. Bellini carcinoma is highly aggressive, and the majority of patients present with advanced disease upon first diagnosis [29,30].

1.3.6. SMARCB1-deficient medullary renal cell carcinoma

Renal medullary carcinoma is a high-grade adenocarcinoma characterized by loss of SMARCB1. It is predominantly observed in patients with African ancestry and sickle cell traits or disease. The tumour formation is most likely triggered by the hypoxic environment of the renal medulla, worsened by the microvascular occlusion by the sickle-cell shaped erythrocytes [31] Prognosis is extremely poor with a median overall survival of approximately 8 months [32].

Table 2 - Common histologic RCC subtypes, morphological characteristics, and molecular alterations [33]

Tumour type	Gross Appearance	Microscopic Appearance	Known somatic alterations	Cytogenetic alterations
Clear cell	Yellow, well circumscribed, and can possess distinct areas of haemorrhage and necrosis	Abundant clear cytoplasm due to deposition of lipid and glycogen	VHL, PBRM1, SETD2, BAP1, JARID1A, mTOR, PI3K	3p (90%), 14q, 8p, and 9p and gains at 5q and 12q
Papillary	Mixed cystic/solid consistency. PapRCC lesions are often reddish-brown and frequently have a well-demarcated pseudocapsule	Papillary or tubulopapillary architecture. Calcifications, necrosis, and foamy macrophage infiltration.	MET, NRF2, CUL3	Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p. Papillary type 2 with gains of 8q, loss of 1p and 9p.
Chromophobe	Large, well-circumscribed, tan-brown tumour with occasional central scar	Distinct cell borders and a voluminous cytoplasm, nuclear morphology with perinuclear halos, binucleation Classic: pale cytoplasm Eosinophilic: large tumour cells with fine eosinophilic granules	TP53	Loss of chromosomes 1, 2, 6, 10, 13, and 17
Oncocytoma	Mahogany colour, well circumscribed, occasional central scar, and rarely with necrosis	Polygonal cell with abundant eosinophilic cytoplasm and uniform, round nuclei	Mitochondrial complex I genes	Loss of 1 p, loss of Y, often normal karyotype
Collecting Duct	Partially cystic, white- grey appearance and often exhibit invasion into the renal sinus	Tubulopapillary pattern, often with cells taking columnar pattern with hobnail appearance, presence of mucinous material, desmoplastic stroma	Unknown	Losses at 8p, 16p, 1p, 9p, and gains at 13q
Medullary	Tan/white, poorly defined capsule, extensive haemorrhage, and necrosis	Poorly differentiated, eosinophilic cells; inflammatory infiltrative cells; sheet-like or reticular pattern common	Unknown	Poorly described but believed normal karyotype.

1.3.8. Sarcomatoid transformation

Sarcomatoid transformation is not considered to be a distinct histological subtype but a feature that can occur in any type of RCC. It occurs in 5% of all RCC resected and approximately 15% of patients with stage IV tumours have additional sarcomatoid histologic features [34]. When present, it is associated with a worse prognosis so it`s presence or absence must be a detailed in every histological report. Microscopical characteristics include spindle-like cells, high cellularity, heightened mitotic activity and necrosis.

1.3.9. Hereditary renal cell carcinoma syndromes

Almost 5% of patients with RCC may harbour hereditary RCC syndromes. The most common hereditary RCC syndromes include VHL syndrome, Birt-Hogg-Dube syndrome, hereditary papRCC, hereditary leiomyomatosis and RCC (HLRCC), succinate dehydrogenase (SDH)-deficient tumour syndromes, BAP1 tumour predisposition syndrome and tuberous sclerosis [35] (**Table 3)**.

Table 3 – Most common hereditary RCC syndromes [33]

Syndrome	Gene Protein	Chromosome	Kidney	Skin	Other organs involved
von Hippel-Lindau	VHL pVHL	3p25	Multiple, bilateral ccRCC, renal cysts	-	Retinal and CNS hemangioblastomas (type 1), phaeochromocytoma (type 2), pancreatic islet cell tumours, neuroendocrine tumours, endolymphatic sac tumours
Hereditary papillary renal carcinoma	c-MET HGF-R	7q31	Multiple, bilateral papRCC	-	-
Hereditary leiomyomatosis and RCC	FH	1q42-43	papRCC	Cutaneous leiomyomas	Uterine leiomyomas and leiomyosarcomas
Birt-Hogg-Dubé	BHD Folliculin	17p11.2	Multiple chRCC, conventional RCC, hybrid oncocytoma, papRCC, oncocytic tumours	Facial fibrofolliculoma	Lung cysts, spontaneous pneumothorax
Tuberous sclerosis	TSC1 Hamartin TSC2 Tuberin	9q34 16p13	Multiple, bilateral angiomyolipomas	Cutaneous angiofibroma	CNS lesions, retinal hamartomas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis.

1.3.10. Other types

There are several other subtypes of RCC which are very rare in presentation and probably doesn't influence the prognosis substantially. Nevertheless, one must be aware that other histologies may also arise from renal parenchyma such as neuroendocrine variants, cystic variants, mesenchymal variants, mixed mesenchymal and epithelial variants. Understanding the histological differences and bimolecular pathways of these RCC subtypes should provide insight into their varying clinical courses and provide us with an estimation of prognosis.

1.4. Staging

The Tumour Node Metastasis (TNM) classification is a universally recognized approach for describing the anatomic extent of malignant tumours [36]. The initial classification and outcome stratification of renal tumours proposed in the sixth edition of the TNM, published in 2002, was validated later in several studies [37–39]. However some suggested that there are still uncertainties especially concerning the locally advanced RCC hence the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) released the seventh edition which took effect on January 1, 2010. (**Table 4.)** This staging system have been validated [40,41] and is a powerful predictor of cancer- specific survival.

Table 4 – TNM classification [33]

T	**Primary tumour**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4.0 cm
T1b	Tumour > 4.0 cm but ≤ 7.0 cm
T2	Tumour > 7.0 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm but ≤ 10 cm
T2b	Tumour > 10 cm
T3	Tumour extends to major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
T3a	Tumour grossly extends into the renal vein, or its segmental (muscle-containing) branches or tumour invades perirenal and/ or renal sinus fat (peripelvic) but not beyond Gerota fascia
T3b	Tumour grossly extends into the vena cava below the diaphragm
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastases in more than one regional lymph node
M	**Distant metastases**
M0	No distant metastasis
M1	Distant metastasis

pTNM Stage Grouping	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 T1, T2, T3 N1 M0
Stage IV	T4, Any N, M0 Any T, Any N, M1

1.5. Diagnostic evaluation

1.5.1. Symptoms

Today, more than half of renal masses are discovered incidentally due to the widespread utilization of abdominal imaging techniques such as ultrasonography and cross-sectional imaging [42]. Historically, patients presented with the classic triad of palpable flank or abdominal mass, pain, and gross haematuria. When present, these findings correlate with aggressive histology and advanced disease [43,44]. Approximately 40% of the patients present with systemic symptoms such as weight loss, diffuse abdominal pain, anorexia, fatigue, and fever. RCC may induce paraneoplastic syndromes including hypercalcemia or hypertension [45].

1.5.2. Physical examination

Standard physical examination is little to no help in diagnosing RCC. However, patients with palpable abdominal mass or cervical lymphadenopathy rapidly undergo radiological imaging. Men with acute onset of varicocele or lower extremity oedema being indicative of a retroperitoneal mass compressing the renal vein must also undergo further examinations.

1.5.3. Laboratory findings

A standard laboratory assessment with the following parameters should be performed: serum creatinine, glomerular filtration rate (GFR), complete blood count, liver function test, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium and urine analysis [46,47].

1.5.4. Imaging investigations

The majority of renal tumours are detected through abdominal ultrasound or computed tomography, which are typically conducted for unrelated purposes [48]. Computed tomography imaging must be performed before and after injection of contrast material with consecutive measurement of Hounsfield units (HUs). An increase of ≥ 15 HUs signifies enhancement and serves as confirmation of a malignant lesion [49]. A computed tomography scan of the abdomen also allows to determine the primary tumour extension, potential venous involvement, enlarged locoregional lymph nodes and detect the presence of other solid organ metastasis.

1.5.5. Renal tumour biopsy

Percutaneous renal tumour biopsy can be performed to obtain a histological diagnosis from indeterminate renal masses and for patients who are candidates for active surveillance. In case of metastatic disease, it can help select the systemic therapy option [50,51].

1.6. Prognostic factors

1.6.1. Histological factors

Over the years, multiple prognostic factors have been identified and used to better characterise patient survival. One of these factors is the histological subtype of RCC. It has been investigated in a series of multicentre, international studies with large patient population [52,53]. Despite the large number of cases, study results are inconsistent. Some authors identify the histological subgroup as an independent prognostic factor [54], while others have seen no association between RCC subtypes and survival rates [55]. In a multicentre study conducted by Steffens et al. the authors compared the incidence and the long-term prognosis of papillary and clear cell RCC. They analysed almost 5000 patients who received either radical nephrectomy or nephron-sparing surgery at five centres in Germany. Their study showed that patients localized papRCC have better prognosis and those with advanced or metastatic papRCC demonstrated worse outcomes compared to ccRCC [52].

Tumour grade stands as one of the foremost histological prognostic indicators. The Fuhrman nuclear grade, previously the most commonly employed grading system, has largely been substituted by the WHO/ISUP grading classification.

Nuclear grade is an important prognostic factor and is integrated in multiple prognostic tools. The previously used Fuhrman nuclear grade has been replaced by the WHO/ISUP grading classification [56]. Compared to the Fuhrman grading which took into account the nuclear size, nuclear shape, and nucleolar prominence [57], the WHO/ISUP only examines nucleolar prominence for grade 1-3 tumours. This provides superior prognostic information [58] and allowed for less interobserver variation [59]. Tumours with rhabdoid and sarcomatoid features can be found in all RCC subtypes and are equivalent to grade 4 tumours. The WHO/ISUP grading system is applicable to both ccRCC and papRCC, however currently not recommended for chromophobe RCC.

1.6.2. Prognostic models

Multiple prognostic models have been developed in the organ-confined disease setting, after surgical resection. These have subsequently been externally validated and are widely used in the current clinical practice [60–65].

In the metastatic setting, risk groups have been determined either by the by the Memorial Sloan Kettering Cancer Centre risk classification (MSKCC) [66] or the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification [67,68].

The MSKCC prognostic system was created from data collected from 670 patients, treated with targeted therapy. The aim of this study was to identify prognostic factors which when combined, are able to predict survival in patients with metastatic RCC. Five prognostic factors have been identified:

- low Karnofsky performance status (<80%),
- elevated LDH (> 1.5x upper limit of normal),
- low serum haemoglobin (< lower limit of normal),
- elevated 'corrected' serum calcium (>10mg/dL),
- time from initial RCC diagnosis to start of systemic therapy <1 year.

Based upon these baseline features, patients with metastatic RCC can be categorised into three risk groups:

- favourable (no risk factors, median survival 30 months),
- intermediate (1-2 risk factors, median survival 14 months),
- poor (≥ 3 risk factors, median survival 6 months).

Given that the MSKCC risk model was developed in patients receiving cytokine therapies, new attempts to identify novel prognostic factors in the era of targeted therapies have been ongoing and in 2009 Heng at al. developed the IMDC prognostic model.

This prognostic model was developed using data from 645 patients treated with anti-VEGF therapy. Four characteristics from the MSKCC risk model were independent predictors of survival:

- haemoglobin less than the lower limit of normal,
- corrected calcium greater than the upper limit of normal,
- Karnofsky performance status less than 80%,
- time from diagnosis to treatment of less than 1 year.

In addition,

- neutrophils greater than the upper limit of normal
- platelets greater than the upper limit of normal

were additional independent adverse prognostic factors. Patients were divided into three risk categories:

- favourable risk group (no prognostic factors, median OS (mOS) was not reached),
- intermediate risk group (1-2 prognostic factors, mOS of 27 months),
- poor risk group (≥ 3 prognostic factors, mOS of 8.8 months).

The IMDC risk score has been employed in all the recent randomised clinical trials, including those using immune checkpoint inhibitors (ICIs), making it the preferred method for risk stratification in routine clinical practice.

1.7. Treatment of localised RCC

Surgical resection is the only curative treatment for localised RCC. Based on currently available oncological and quality of life data, nephron sparing surgery is the preferred option in organ confined tumours irrespective of the surgical approach (open, laparoscopic, or robot-assisted). Partial nephrectomy is recommended in all T1 tumours if negative margins can be obtained [69,70]. In case of locally advanced disease or if a partial resection is not feasible, an open or

laparoscopic radical nephrectomy should be carried out. If the preoperative staging doesn't show any evidence of lymph node involvement, additional lymph node dissection does not confer any survival benefit [71]. Cryo- or radiofrequency ablation are possible treatment options in patients with small renal masses (≤4 cm), especially in frail patients with high surgical risk, or other significant morbidities [72,73]. Active surveillance may be considered for elderly patients (age ≥ 75) with significant comorbidities [74].

1.8. Treatment of locally advanced RCC

Radical nephrectomy with negative margins remains the gold standard treatment for RCC. Systematic adrenalectomy or lymph node dissection is not recommended if there is no local invasion [71,75]. In case of clinically positive lymph nodes, lymphadenectomy is justified [76] although no survival benefit has been demonstrated [77].

The use of neoadjuvant therapy is still experimental and should not be routinely recommended to downsize tumours outside of clinical trials. Multiple prospective, randomized clinical trials investigated the use of adjuvant VEGFR or mTOR inhibitors in patients with locally advanced, high risk RCC. The ASSURE study randomized patients with high risk RCC to receive sunitinib, sorafenib or placebo. No difference was found in 5-year disease-free survival (DFS) (47.7%, 49.9%, 50.0%, respectively for sunitinib, sorafenib, placebo) or overall survival (OS) rates (75.2%, 80.2%, 76.5%, respectively) between the 3 arms [78].

In the PROTECT study, patients with high-risk RCC were randomized to receive either pazopanib or placebo. There was no improvement of DFS when looking at patients receiving pazopanib 600mg (HR: 0.86, 95% CI: 0.7–1.06, p = 0.16), however DFS was improved when patients received the full dose of pazopanib 800mg (HR: 0.69, 95% CI: 0.51–0.94, p = 0.02). There was no benefit in OS in either of the groups [79].

The ATLAS study, a phase III double-blind, randomized, phase III study investigated axitinib vs placebo. The trial was stopped due to futility. There was no statistically significant difference in DFS (HR: 0.870, 95% CI: 0.660–1.147, p = 0.3211). Overall survival data were not mature [80].

The S-TRAC study randomised patients with high risk RCC post-surgery to either sunitinib or placebo. There was a significant benefit in DFS with sunitinib (HR: 0.76, 95% CI: 0.59–0.98, p = 0.03) [81]. The updated results showed a continued benefit in DFS (HR: 0.74, 95% CI: 0.55–0.99, p = 0.04). The median OS was not reached in either study arms (HR: 0.92, 95% CI: 0.66–1.28, p = 0.6) [82].

Lastly, the SORCE trial which investigated 12- and 36-months of adjuvant sorafenib. No differences were found in DFS or OS rate in patients with high risk RCC [83]. In a recent meta-analysis, which pooled results from all phase III randomized trials exploring adjuvant TKIs in ccRCC, the combined HR for OS was 0.89 (95% CI: 0.76–1.04), and for DFS, it was 0.84 (95% CI: 0.76–0.93) [84]. In summary, adjuvant use of TKIs does not result in significant OS benefit, however, is associated with increased DFS rates high-risk patients.

Multiple, prospective, randomized trials have been investigating the use of immune checkpoint inhibitors in the adjuvant setting. These include the programmed death receptor-1 inhibitors nivolumab (PROSPER; NCT03055013), pembrolizumab (KEYNOTE-564; NCT03142334), as well as the programmed death ligand-1 inhibitors atezolizumab (IMmotion010;

NCT03024996) and durvalumab (RAMPART [Renal Adjuvant Multiple Arm Randomised Trial]; NCT03288532). Currently, two of the trials has read out.

The Keynote-564 trial evaluated pembrolizumab vs. placebo as adjuvant therapy in patients with intermediate (pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0, M0) or high-risk disease (pT4, any grade, N0 M0; or pT any stage, and grade, or N+, M0), or M1 without any evidence of disease after primary tumour and metastases were completely resected [85]. Disease-free survival was improved with pembrolizumab compared to placebo (HR 0·63 [95% CI 0·50−0·80]). Median DFS was not reached in either group [86].

IMmotion010, a phase III, randomized, placebo-controlled, double-blinded trial, evaluated adjuvant atezolizumab in patients with high risk RCC. The median DFS was 57.2 months (95% CI 44.6, NE) for atezolizumab and 49.5 months (95% CI 47.4, NE) for placebo (HR 0.93, 95% CI 0.75, 1.15; p = 0.495). Overall survival was immature [87].

1.9. Treatment of advanced/metastatic RCC

1.9.1. Surgical treatment of the primary tumour in metastatic RCC

In the cytokine era, cytoreductive nephrectomy (CN) was the treatment of choice in patients with single- or oligo-metastatic disease, good performance status or when presenting with a high-volume primary lesion. It is not recommended in patients with poor performance status, or high metastatic volume [88].

Two randomized trials have investigated the role of CN in the era of VEGF targeted therapy. CARMENA, a phase III trial investigated immediate CN followed by sunitinib vs. sunitinib alone. The trial demonstrated that OS was similar in the sunitinib group vs those with CN followed by sunitinib both in intermediate and poor risk (HR: 0.89, 95% CI: 0.71–1.10). Median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82, 95% CI: 0.67–1.00) [89].

The SURTIME study randomized patients with metastatic ccRCC to undergo either immediate CN followed by sunitinib vs 3 cycles of sunitinib followed by CN and continued sunitinib in those without disease progression. The independent data monitoring committee recommended the trial to stop due to poor accrual. Deferred CN did not improve the 28-week progression-free rate (42% in the immediate CN arm vs 43% in the deferred CN arm; p = .61) which was the updated primary endpoint of the trial. The median OS in the deferred and immediate CN arms was 32.4 months (95% CI, 14.5-65.3 months) and 15.0 months (95% CI, 9.3-29.5 months), respectively with a HR of 0.57 (95% CI, 0.34-0.95; p = .03) [90].

These two studies support earlier findings that upfront sunitinib therapy followed by CN is a safe treatment option [91,92]. CN should not be offered to patients with poor ECOG-PS or IMDC poor risk or high metastatic volume [93].

1.9.2. Local therapy of metastases

The most common metastatic sites of RCC are lung, bone, liver, and brain, but can occur at any anatomical site [94]. Local treatments such as metastasectomy, conventional radiotherapy or stereotactic radiosurgery remain controversial in the treatment of metastatic RCC. A systematic

review was conducted to determine the benefit of additional local interventions in this setting. In summary, patients undergoing complete metastasectomy had longer OS and better symptom control than those having incomplete or no metastasectomy [95]. These modalities can be considered for selected patients after multidisciplinary team discussion.

1.10. Systemic therapy for advanced/metastatic RCC

Clear- cell histology remains the most common type of RCC hence the majority of pivotal studies have been conducted in this patient population.

1.10.1. Targeted therapies

The development of ccRCC is closely linked to a mutation occurring in the von Hippel-Lindau (VHL) gene, located on chromosome 3p. Inheriting a mutated VHL allele leads to VHL disease which constitutes the primary cause of inherited ccRCC. Furthermore, as many as 75% of sporadic ccRCC exhibit abnormalities in the VHL gene, consequently, the loss of VHL function is a significant event in the development of RCC [96]. If there is an aberrant VHL, there is an accumulation of hypoxia-inducible factor (HIF), resulting in the production of various growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, erythropoietin. VEGF (particularly VEGF-A, VEGF-C, VEGF-D) promote neoangiogenesis by activating intracellular signalling pathways via specific receptors VEGF receptors (VEGFRs) equipped with tyrosine kinase activity **(Figure 1).** Several drugs targeting this pathway have regulatory approval and are used in everyday practice.

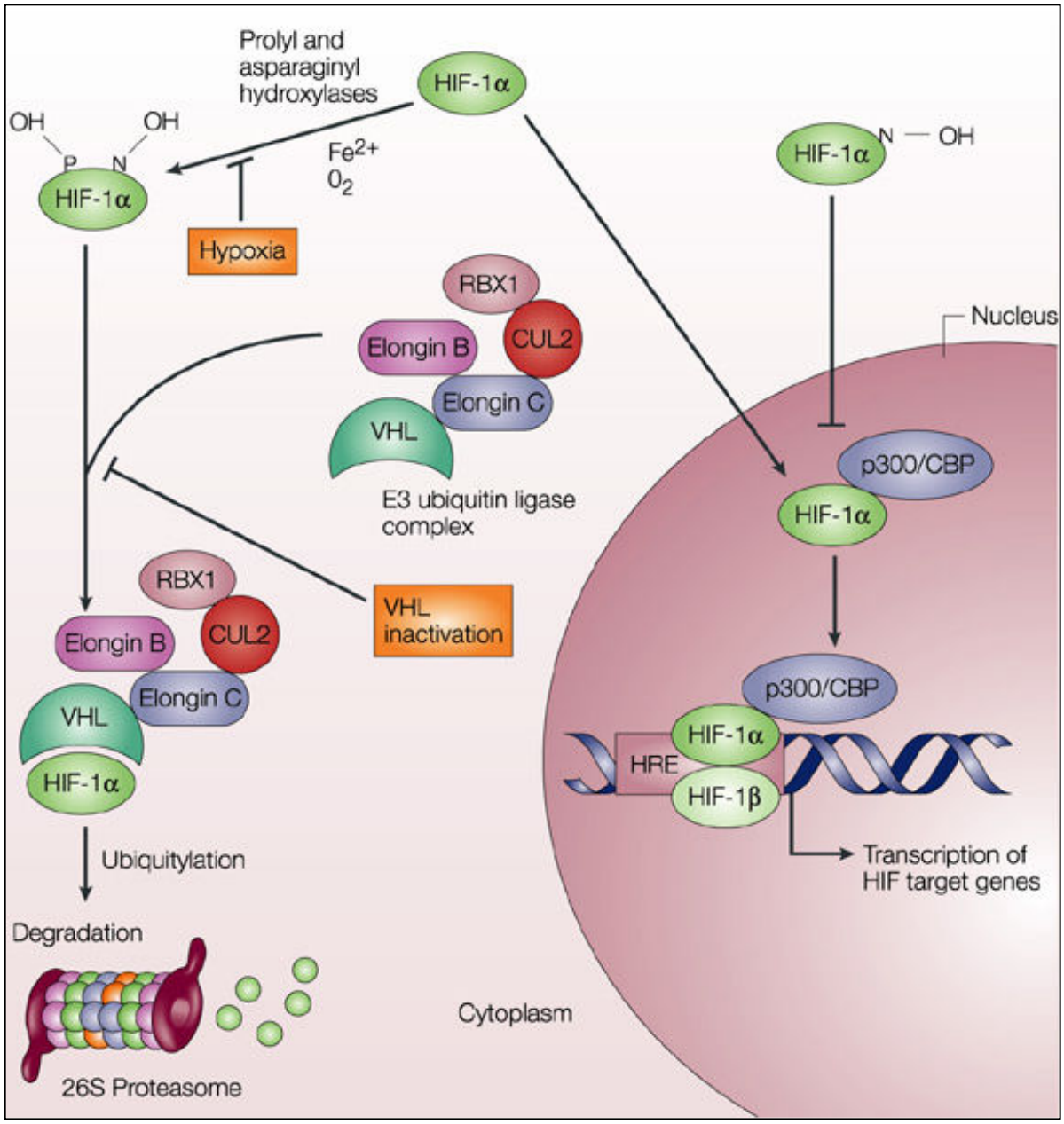


Figure 1 *- Von Hippel–Lindau dysregulation pathway [97]*

Figure 2 shows the known dysregulation pathways of RCC and currently available treatment options.

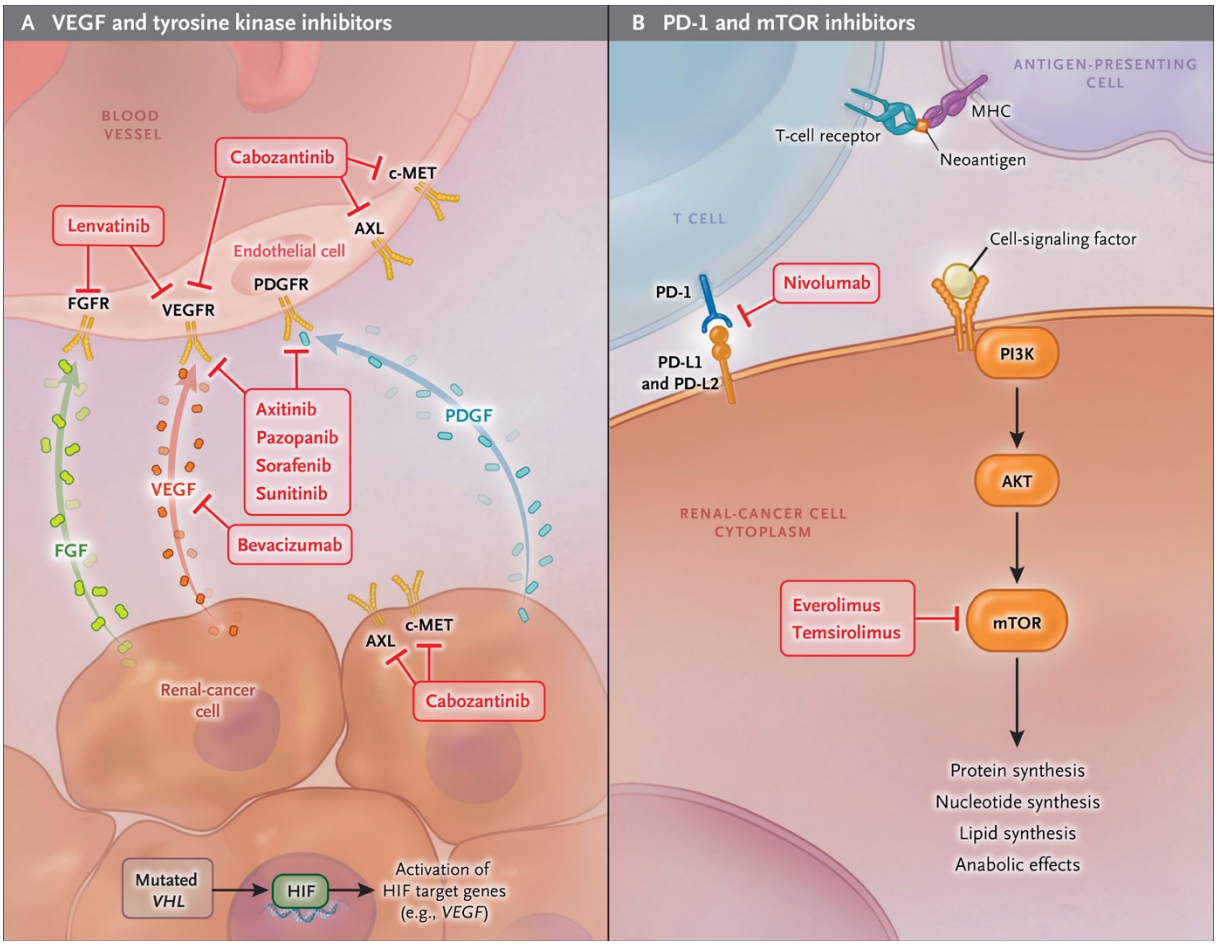


Figure 2 *- Pathways and currently approved medical treatments in metastatic renal cell carcinoma [98]*

1.10.1.1. Tyrosine kinase inhibitors

Sorafenib is an oral multikinase inhibitor of VEGFR, PDGF and Raf family kinases. In 2007, Escudier et al. showed that compared to placebo, treatment with sorafenib prolongs PFS in patients with advanced ccRCC who failed previous immunotherapy. The median PFS was 5.5 months in the sorafenib arm compared to 2.8 months in the placebo arm (HR: 0.44, 95% CI: 0.35–0.55, $p < 0.01$) [99].

Sunitinib inhibits all receptors for PDGF and VEGFRs thus demonstrating an anti-tumour and an anti-angiogenic activity. The simultaneous inhibition of these targets therefore reduces tumour vascularisation and triggers cancer cell apoptosis and results in tumour shrinkage. In a phase III study by Motzer, median PFS was significantly longer in patients receiving sunitinib than those receiving IFN-α (11 vs. 5 months). Median OS was higher in patients treated with sunitinib vs. IFN-α (26.4 vs 21.8 months, respectively) with a HR of 0.65 (95%CI, 0.45-0.94; p=0.02). The sunitinib group also showed a higher objective response rate than patients treated with IFN-α (31% vs. 6%, p<0.001). The number of patients with grade 3 or 4 treatment-related fatigue was significantly increased in the IFN-α group, whereas diarrhoea was more frequently observed in the sunitinib group [100].

Pazopanib is a tyrosine kinase inhibitor (TKI) (with c-KIT, FGFR, PDGFR and VEGFR activity). A phase III study of patients of metastatic RCC treated with pazopanib demonstrated a significant improvement in PFS and response compared to placebo in both treatment-naive

and cytokine-pre-treated patients. Median PFS for pazopanib compared to placebo was 9.2 vs. 4.2 months with a HR of 0.46 (95%CI, 0.34-0.62; p< 0.0001) [101].

A trial comparing pazopanib and sunitinib (COMPARZ) established pazopanib as another first-line treatment in metastatic RCC. Both drugs showed similar PFS and OS rates.

Patients in the sunitinib arm had a higher rate of fatigue (63% vs. 55%), hand–foot syndrome (50% vs. 29%), and low platelet count (78% vs. 41%); patients in the pazopanib arm had higher rates of elevated liver enzymes (60%, vs. 43% with sunitinib) [102]. The PISCES study showed that there was a higher patient preference for pazopanib compared to sunitinib (70% vs. 22%, $p < 0.05$) due to treatment-related adverse events [103].

Axitinib is a second-generation inhibitor of VEGFR-1, -2, and -3. The AXIS trial compared axitinib to sorafenib in the treatment-refractory setting. The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib (HR 0.665; 95% CI, 0.544-0.812; p<0.0001). The most common treatment-related adverse events included diarrhoea, hypertension, and fatigue in the axitinib arm; diarrhoea, palmar-plantar erythrodysesthesia, and alopecia in the sorafenib arm [104]. Final analysis of OS showed no significant differences between axitinib or sorafenib [105]. In a randomised phase III trial of axitinib vs. sorafenib in treatment-naïve patients, there was no significant difference in median PFS between the two treatment groups and as a result axitinib was not approved in the first-line setting [106].

Cabozantinib is another TKI targeting c-Met and VEGFR2. A randomised phase III trial comparing cabozantinib vs. everolimus in patients with treatment-refractory ccRCC (METEOR) demonstrated a median PFS for cabozantinib of 7.4 (95% CI, 5.6-9.1) months vs. 3.8 (95% CI, 3.7-5.4) months for everolimus. The objective response rate for cabozantinib and everolimus were 21% and 5% (p<0.001), respectively. Grade 3/4 adverse events were higher in the cabozantinib arm (74%) vs everolimus (65%) [107].

The phase II, CABOSUN study randomised patients with treatment naïve, intermediate- or poor-risk ccRCC to cabozatinib or sunitinib. There was a significantly higher overall response rate (46% vs 18%) and PFS (8.2 vs. 5.6 months, adjusted HR: 0.66, 95% CI: 0.46 to 0.95; p = 0.012) in the cabozantinib group. There was no difference in OS. Toxicity was similar in both groups [108,109].

Lenvatinib is another multi-TKI of VEGF receptor family with inhibitory activity against fibroblast growth factor receptors, PDGFRα, RET, and KIT. A randomised, phase II, multicentre study compared lenvatinib plus everolimus, single-agent lenvatinib, or single-agent everolimus. in previously treated mRCC patients. The combination of lenvatinib and everolimus demonstrated the highest efficacy compared to the other arms [110].

Tivozanib is a selective inhibitor of VEGFR1, VEGFR2, and VEGFR3. Two randomized phase III trials explored the efficacy of tivozanib compared to sorafenib. In both studies, patients in the tivozanib arm had a higher PFS, however no differences were seen in OS [111,112].

1.10.1.2. Monoclonal antibody against circulating VEGF

Bevacizumab is a recombinant humanised monoclonal antibody which inhibits VEGF-A. A phase III trial compared bevacizumab + interferon alfa (IFN-α) with INF-α monotherapy in patients with previously untreated mRCC [113]. The combination therapy showed a significant

improvement in overall response rate and PFS (5.4 months with IFN-α vs. 10.2 months with bevacizumab + IFN-α). In the final analysis, no differences were seen in OS [114].

1.10.1.3. mTOR inhibitors

Temsirolimus is a mammalian target of rapamycin (mTOR) inhibitor. It blocks tumour angiogenesis by reducing synthesis of VEGF. In a multicentre, phase III trial [121], 626 patients with treatment naive mRCC were randomly assigned to receive temsirolimus weekly, IFN-α or a combination of both agents. Patients in the temsirolimus arm had a higher OS (HR 0.73; 95% CI, 0.58 to 0.92; p=0.008) and PFS (p<0.001) than patients in the IFN-α group. There was no difference in OS between the combination and IFN-α arm, but patients presented higher toxicity rates [115].

Everolimus is a derivative of sirolimus. A phase III, randomised, double-blind, placebo-controlled trial (RECORD-1) [116] investigated everolimus in patients with previously treated mRCC. The median PFS with everolimus was 4.0 months (95% CI, 3.7-5.5) vs 1.9 months in the placebo arm (95% CI 1.8-1.9). Another randomised phase II trial, RECORD-3, was conducted to compare first-line everolimus followed by sunitinib (Eve → Su) at progression with the standard sequence of front line sunitinib followed by everolimus (Su → Eve) in patients with mRCC [123]. The median PFS in the Eve → Su group was 7.9 months compared to 10.7 months in the Su → Eve group (HR 1.4; (95% CI, 1.2-1.8)). After cross- over the median combined PFS was 21.1 months for the sequence Eve → Su and 25.8 months for the sequence Su → Eve (HR, 1.3; 95% CI, 0.9 to 1.7). The median OS was also lower (22.4 months) in the Eve → Su group compared to 32.0 months for Su → Eve (HR 1.2; 95% CI, 0.9 to 1.6) [117].

1.10.2. Immunotherapy

1.10.2.1. Cytokine therapies

The treatment of cancer by activation of the immune system against cancers has long been pursued. The increasing understanding about the functioning of our immune system, coupled with progress in recombinant DNA technology, has paved the way for clinical trials involving immune-stimulating cytokines like interferons and interleukins. These trials have led to a small number of durable tumours responses in selected cancers such as melanoma and RCC at the expense of serious toxic effects.

Before the targeted therapy era, immunotherapy was the only available treatment for patients with metastatic RCC. In a study conducted by Escudier et al. the combination therapy of IFN-α and bevacizumab showed a significant improvement in PFS, compared to IFN-α monotherapy [113]. However, studies show that immunotherapy may only be effective in selected groups, including patients with ccRCC, favourable MSKCC risk criteria, and presenting with lung metastases only. Further studies demonstrated a response rate of 6-15% and a 25% decrease in tumour progression risk when compared to placebo [118,119]. Unfortunately, intermediate-risk patients failed to demonstrate the same benefit [120].
Interleukin-2 (IL-2) has been used since the 1980´s to treat metastatic RCC. In 2003, Yang et al. conducted a randomised trial where patients received either high-dose or low-dose IL-2. Major tumour regressions, as well as complete responses, were seen with both regimens. There were less treatment-related adverse events observed with low dose IL-2. There was no difference in OS between the two groups [120].

One constraint in harnessing the immune system to combat cancer lies in its function of preventing autoimmune responses. Cancer takes advantage of this capability by utilizing a set of immune evasion mechanisms originally evolved to prevent autoimmunity. Among these mechanisms is the co-opting of immune cell checkpoints that are triggered upon T-cell activation [121].

1.10.2.2. Immune checkpoint inhibitor therapy

Immune checkpoint inhibitors (ICI) are monoclonal antibodies blocking the inhibitory T-cell receptor Programmed Death-1 (PD-1), its ligand (PD-L1) or the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) signalling to restore tumour specific T cell immunity [122]. The first immune checkpoint inhibitors developed were pembrolizumab and nivolumab targeting the PD-1 receptor, atezolizumab and durvalumab blocking it´s ligand PD-L1, primarily within the tumour microenvironment. Lastly, ipilimumab and tremelimumab target CTLA-4. Currently there are multiple novel immune checkpoint inhibitors in pharmaceutical development or under investigation in ongoing clinical trials.

Single agent immune checkpoint inhibitors were first investigated in the treatment refractory mRCC setting. In the CheckMate 025, patients were randomized to receive single agent nivolumab vs everolimus, after 1-2 lines of previous VEGF-targeted therapy. The trial showed that patients in the nivolumab group had a significantly higher OS (25.0 vs 19.6 months) with a HR of 0.73 (98.5% CI, 0.57-0.93; p = 0.002). Objective response rate and adverse event profile also favoured nivolumab [123]

The use of single agent ICI was also explored in treatment-naïve mRCC patients. The IMmotion 150 study randomized patients to received atezolizumab or sunitinib. Atezolizumab did not improve PFS vs sunitinib (HR of 1.19 (95% CI: 0.82–1.71) [124]. Pembrolizumab monotherapy was investigated in the phase II KEYNOTE-427 trial showing high response rates (38%), but relatively low PFS (8.7 months 95% CI: 6.7–12.2) [125]. Based on above results single agent ICI is not recommended for treatment naïve mRCC.

Subsequently, ICI combinations with PD-1 and CTLA-4 inhibitors were tested in the phase III, randomized trial CheckMate 214. Patients with treatment naïve, intermediate- and poor-risk mRCC were randomized to receive nivolumab and ipilimumab or sunitinib. The combination demonstrated higher OS rates with a HR of 0.63, 95% CI: 0.44–0.89) which led to regulatory approval in the US and Europe [126]. The 5-year follow up data of the study showed continued OS (HR 0.68 (95%CI: 0.58–0.81)) and response rate benefit in the combination ICI arm[127].

Combination of ICI with VEGF targeted therapy represented the next milestone and results of the below trials changed the treatment landscape of mRCC.

In the phase III, randomized KEYNOTE-426 study, patients with treatment-naive metastatic ccRCC received pembrolizumab + axitinib or sunitinib monotherapy. Pembrolizumab + axitinib showed a significantly improved median OS (45.7 vs 40.1 months; HR 0.73, 95% CI 0.60-0.88) in all three IMDC risk groups. Similarly, patients in the pembrolizumab + axitinib group also had higher PFS (HR 0.68 (95%CI: 0.58-0.80)) and higher objective response rate (60.4% vs 39.6%; p < 0.0001) [128,129].

In the phase 3 CheckMate 9ER trial, patients with front line mRCC received nivolumab plus cabozantinib versus sunitinib. The combination nivolumab + cabozantinib demonstrated

superiority over sunitinib in terms of OS improvement (HR 0.70, (95% CI 0.55–0.90)), PFS benefit (HR 0.56, (95% CI 0.46–0.68)) and response rate (55.7% vs 28.4%) [130,131].

The JAVELIN Renal 101 trial recruited patients with treatment naïve mRCC and explored the combination of avelumab/axitinib vs. sunitinib. The combination arm demonstrated improvements in PFS (HR 0.69 (95% CI: 0.56–0.84)) and higher objective response rates compared to sunitinib (51.4% vs 25.7%). The trial has not shown a significant OS advantage [132].

The phase 3 CLEAR trial recruited patients with newly diagnosed mRCC and randomized them in a 1:1:1 fashion to receive lenvatinib/everolimus or lenvatinib/pembrolizumab vs sunitinib. Randomization was stratified by IMDC prognostic groups. There was a significantly higher PFS in the lenvatinib/pembrolizumab, group compared to sunitinib (22.1 vs 11.1 months; HR 0.38, 95% CI 0.23, 0.62) as was OS (HR 0.71, 95% CI 0.30, 1.71). Additionally, ORR was was almost double with lenvatinib/pembrolizumab, compared to sunitinib (71% vs 36%) [133].

The COSMIC-313 study investigated triplet combination therapy with VEGF TKI and ICIs. In this double-blind, randomized phase III trial, patients with treatment naïve mRCC with IMDC intermediate or poor risk disease were randomly assigned to receive either ipilimumab/nivolumab in combination with cabozatinib or ipilimumab/nivolumab and placebo. The study successfully met its primary endpoint by demonstrating a significant improvement in PFS (HR 0.73, 95% CI, 0.57–0.94; p=0.013) in the triplet arm. The overall response rate was also higher in the cabozantinib arm (43%) compared to placebo (36%). Follow-up for OS is ongoing [134].

1.10.3. Therapeutic strategies

1.10.3.1. Treatment naïve setting

Based on currently available data, immunotherapy combinations either with PD-1/CTLA-4 or ICIs with VEGF inhibitors constitute the treatment of choice in patients with treatment naïve clear cell mRCC. Pembrolizumab/axitinib, nivolumab/cabozantinib and lenvatinib/pembrolizumab are standard of care in all IMDC-risk patients and ipilimumab/nivolumab is recommended in IMDC intermediate- and poor-risk patients. Front-line VEGF inhibitors sunitinib, pazopanib (in all IMDC risk groups), and cabozantinib (IMDC intermediate- and poor-risk disease), are alternative treatment options in patients with a contraindication for immune checkpoint inhibitor-based therapy (**Fig. 3**) [135].

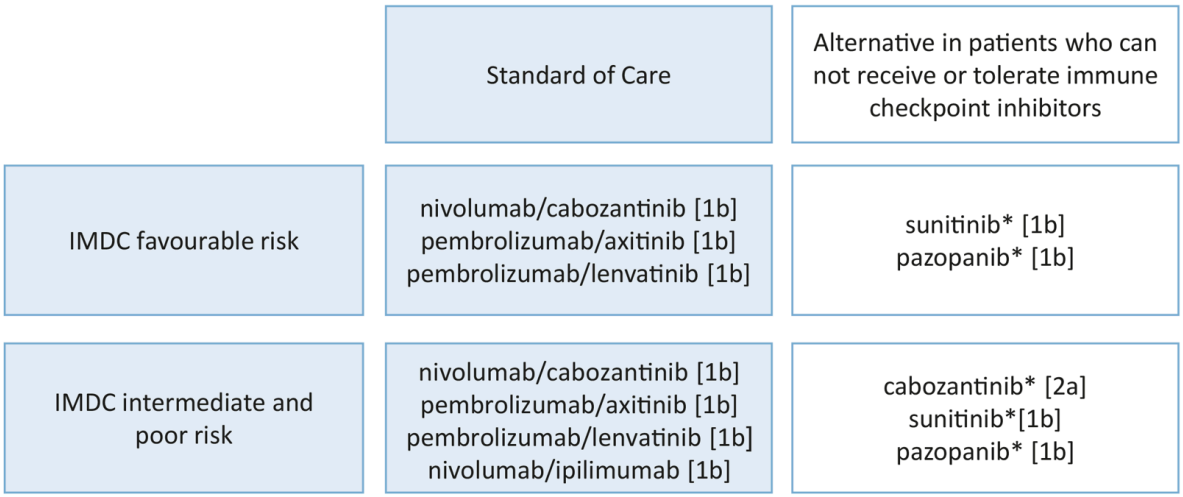


Figure 3 - Treatment algorithm for patients with treatment naïve metastatic ccRCC *[135]*

1.10.3.2. Treatment- refractory setting

Therapy options in the **treatment- refractory setting** have been dramatically modified by the approval of multiple immunotherapy and ICI/VEGF combinations which are currently used in the front-line setting (**Fig. 4).** Randomised data in this treatment-refractory setting is lacking. There are a number of publications looking at retrospectively collected data on single agnet VEGFR-TKI therapy, but these data come with notable limitations. Overall, patients who failed previous immunotherapy in the first line setting should proceed with any VEGF- targeted therapy that has not been previously used. Patients who received single agent VEGF- targeted therapy in the treatment naïve setting, should receive either second line nivolumab or cabozantinib [106,123,136].

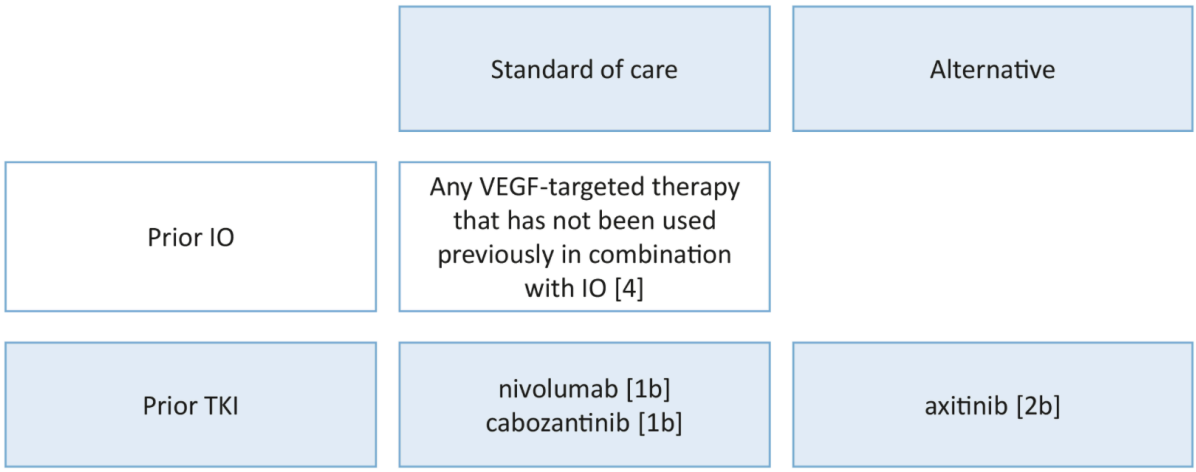


Figure 4 - Sequencing algorithm for patients with metastatic ccRCC who failed previous therapies [135]

1.10.4. Therapeutic strategies for metastatic papillary renal cell carcinoma

There are no randomized, phase III trials investigating therapies in patients with papRCC. Evidence is derived from small single-arm trials, expanded access schemes and subgroup analysis of larger studies. Sunitinib and everolimus have been investigated in this patient

population [137–141]. RAPTOR, a phase II trial investigating first line, single agent everolimus in papRCC showed a median PFS of 3.7 months and a median OS of 21.0 months [141].

PAPMET is randomised phase II trial that compared sunitinib to cabozantinib, crizotinib and savolitinib in patients with metastatic papRCC. There was a significantly longer PFS in the cabozantinib group (9.0 months, 95% CI: 6–12) compared to sunitinib (5.6 months, CI: 3–7; HR 0.60 [0.37–0.97, p = 0.019]). Response rate for cabozantinib were equally higher 23% vs. 4% (p = 0.010). Savolitinib and crizotinib did not show any benefit when compared to sunitinib [142]. These results underline the role of cabozantinib as a treatment option in patients with papRCC.

Savolitinib is a highly selective MET inhibitor which was investigated in the SAVOIR trial as first-line treatment in MET-driven tumours. These were defined as chromosome 7 gain, MET amplification, MET kinase domain variations or hepatocyte growth factor amplification. Results showed higher efficacy of savolitinib compared to sunitinib (mPFS 7.0 months, 95% CI: 2.8 months-NR vs. 5.6 months, 95% CI: 4.1–6.9 months, HR: 0.71, 95% CI: 0.37–1.36, OS HR: 0.51,94% CI: 0.21–1.17, RR: 27% vs. 7%, for savolitinib and sunitinib, respectively). The median OS for savolitinib was NR. However, the trial was stopped early, due to poor recruitment [143].

Immune checkpoint inhibitors were also investigated in this population. In a single-arm, phase II study first line pembrolizumab treatment resulted in an ORR of 29%, a PFS of 5.5 months (95% CI: 3.9–6.1 months) and OS of 31.5 months (95% CI: 25.5 months-NR) [125].

Just as with ccRCC, combination of ICI and VEGF- targeted therapies have also been investigated in papRCC patients. CALYPSO is a single arm phase II trial that explored durvalumab (PD-L1 inhibitor) and savolitinib in treatment naïve or previously treated patients with metastatic papRCC. Response rate was 29% (95%CI: 16%-46%) in the overall patient population, however this increased to 53% (95% CI: 28%-77%) in MET-driven patients and was 33% (95% CI: 17%-54%) in PD-L1 positive tumours. Median PFS was 4.9 months (95% CI: 2.5-10.0) in the treated population and 12.0 months (95% CI: 2.9-19.4) in MET-driven patients. Median OS was 14.1 months (95% CI: 7.3-30.7) in the treated population and 27.4 months (95% CI: 9.3-NR) in MET-driven patients [144].

Similarly, to the CheckMate 9ER study which explored the combination nivolumab/cabozantinib in ccRCC, these agents were also investigated in patients with non-clear cell disease. A recently reported phase II trial which included 32 (80%) papRCC patients showed an ORR of 47.5% (95% CI, 31.5-63.9), with median PFS of 12.5 months (95% CI, 6.3 to 16.4) and median OS of 28 months (95% CI, 16.3-NE) [145].

Finally, KEYNOTE-B61 is a single arm, phase II study investigating the combination therapy of lenvatinib/pembrolizumab in patients with treatment naïve non-clear cell mRCC. Of the 82 treated patients with sufficient follow up, 51 (62%) had papRCC. Response rate in the overall population was 47.6% (95%CI: 36.4-58.9) and 52.9% (95%CI: 38.5-67.1) in patients with papRCC. The 6-month PFS rate in all treated patients was 72.3% (95% CI, 60.7-81.0) and the 6-month OS rate was 87.8% (95% CI, 78.5-93.2) [146].

2. AIM OF THE DISSERTATION

The aim of this dissertation was to analyse the outcome of patients with metastatic, type 2, papRCC who were received systemic therapy between 2005 and 2015. We aimed to compare the effectiveness of different therapy options with regards to response, PFS and OS.

The following questions are discussed in detail:

- baseline clinical and tumour characteristics of patients with metastatic, type 2, papRCC,
- patient characteristics influencing outcomes,
- systemic therapies used in patients with metastatic, type 2, papRCC,
- response to therapy according to different treatment regimens,
- progression-free survival with targeted agents,
- overall survival with targeted agents.

3. MATERIALS AND METHODS

3.1. Patients

A retrospective analysis was conducted on patients treated at the Department of Urology in the University Hospital Munich Grosshadern, Ludwig-Maximilians University between January 2005, and December 2015. Eligible patients included those with histologically confirmed metastatic, type 2, papRCC, receiving treatment in the department.

The histological workup was determined in every case by using The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia [16] by dedicated genitourinary pathologists. Staging was based on the TNM Cancer Classification System 2016.

Baseline demographic, clinical, and histopathological data were captured in our institutional database. These were correlated with treatment type and outcome. Laboratory tests included haematology, serum chemistry, and coagulation. Tumour assessment was performed using computed tomography or resonance magnetic imaging of the brain, chest, abdomen, and pelvis. Patients were followed from the time of initiation of systemic therapy, until death or end of data collection.

3.2. Procedures and therapies

If clinically indicated, patients underwent partial or radical nephrectomy for the treatment of the primary tumour. This was either performed in the non-metastatic setting or as CN in patients presenting with upfront metastatic disease. The surgery was performed either at our institution or at other urological departments.

Subsequently, all patients received systemic therapy; either using a VEGF inhibitor (sunitinib, sorafenib, pazopanib, axitinib), an mTOR inhibitor (everolimus, temsirolimus) or an immune checkpoint inhibitor (nivolumab).

Sunitinib was administered orally in 6-weekly cycles at a once- daily dose of 50mg for 4 weeks followed by 2 weeks of therapy break. Sorafenib was given at a twice-daily dose of 400mg orally. Temsirolimus was administered intravenously in a dose of 25g on a weekly schedule. Pazopanib was given at a once- daily dose of 800mg continuously, everolimus in once- daily dose of 10mg and Axitinib 5 mg twice-daily. In case of drug toxicity, the dosage was reduced or temporarily withheld. In case of disease progression, the drug was discontinued and if possible, changed to a new line of therapy.

Blood tests were performed every 12 weeks or sooner if clinically indicated for treatment monitoring. These included sodium, potassium, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, AST, ALT, GLDH, cholinesterase, amylase, lipase, creatine kinase, troponin- t, myoglobin, lactate dehydrogenase, cholesterol, triglycerides, uric acid, calcium, inorganic phosphate, magnesium, iron, transferrin, ferritin, total protein, albumin, c-reactive protein, procalcitonin, , glucose, plasma osmolality, prothrombin time, INR, APTT, fibrinogen activity, antithrombin, white blood cell count, red blood cell count, haemoglobin, haematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, chloride, LDL cholesterol, VLDL cholesterol, HDL− cholesterol, HbA1c, differential blood count, TSH, free T4, free T3, BNP and proBNP.

Response to treatment was assessed by computed tomography of the chest, abdomen, and pelvis with administration of contrast when kidney function allowed, in 12 weekly intervals or sooner if necessary. An additional CT scan of the head was performed at baseline. Patients with previously treated or untreated central nervous system metastasis underwent 12 weekly CT of the head. In patients with poor kidney function (stage IV chronic kidney disease or a glomerular filtration rate < 30ml/min) imaging was performed using a native CT scan of the chest and a magnetic resonance imaging of the abdomen and pelvis.

3.3. Outcomes

The primary objective of this study was to give a comprehensive description of patients with metastatic, papillary, type 2 RCC receiving standard of care systemic therapy. The following analysis were carried out:

- description of clinical characteristics,
- overall response rate (ORR) was defined as the percentage of patients achieving complete response (CR) or partial remission (PR) based on cross-sectional imaging,
- DFS was defined as the time from surgery in the curative setting to initiation of systemic therapy in the metastatic setting,
- PFS was defined as the time from treatment initiation to disease progression or death as a result of any cause.
- OS was defined as the time from treatment initiation to death as a result of any cause.

For both time-to event outcomes, patients were censored at the time of last follow-up if an event had not occurred.

The duration of follow-up was calculated from the date of initial diagnosis to the date of death or last follow-up. Information about the exact date of death for each patient was collected retrieved from the patient's hospital record or publicly available data.

3.4. Statistical analysis

Descriptive statistics were used to elucidate baseline clinical and pathologic characteristics, including the mean, median and range for continuous variables and frequency and percentage for categorical variables. Multivariate Cox regression models were used to assess the association between baseline clinico-pathological characteristics (i.e., age, ECOG, MSKCC and IMDC risk groups etc) and upfront metastatic disease or OS. Associations between MSKCC- IMDC risk stratification, tumour stage, Fuhrman grade, type of surgery and clinical factors were performed using Chi-square, Mann Whitney, and Kruskal-Wallis tests.

Survival analyses (DFS, PFS, OS) were performed using the Kaplan-Meier and log-rank methods with a significance level of $\alpha = 0.05$. Statistical analyses were performed using SPSS version 25.0. (IBM, Armonk, NY, USA). In all tests, a p-value < 0.05 was considered as statistically significant.

4. RESULTS -

4.1. Patient and tumour characteristics at first diagnosis

Between January 2005 and December 2015, 228 patients were treated with papillary renal cell carcinoma in the Department of Urology, University Hospital Munich Grosshadern, Ludwig-Maximilians University. Of these, 18.4% (42/228) had metastatic, type 2 papRCC and were treated in our outpatient, specialized, advanced RCC clinic.

Two-third of the patients (67%, 28/42) were male. The median age upon first diagnosis was 60 years (range, 31 -76) **(Fig. 5).** The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 35% (15/42), 1 in 57% (24/42) and 2 in 7% (3/42) of patients.

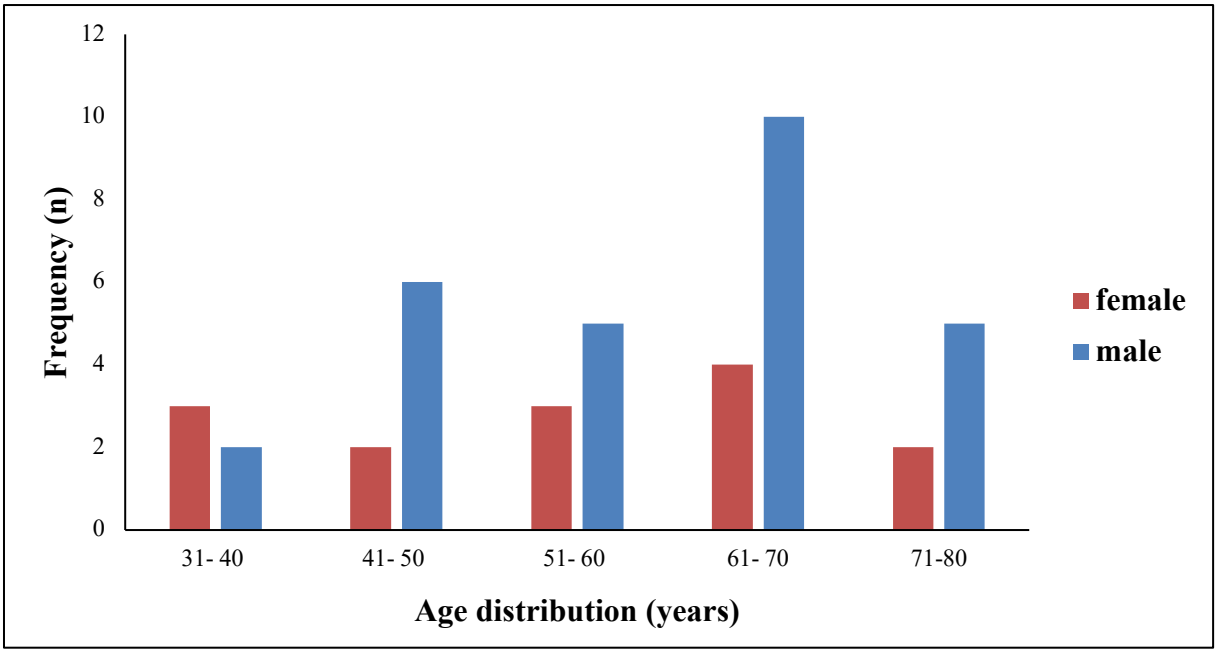


Figure 5 *– Age and gender distribution upon first diagnosis of type 2, papRCC*

Next, we analysed the distribution of patients in both the Memorial Sloan Kettering Score for Metastatic Renal Cell Carcinoma (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups. In our patient population, 19% (8/42), 62% (26/42) and 19% (8/42) had favourable, intermediate, and poor risk disease according to the MSKCC (Motzer) Score. When stratifying patients according to the IMDC risk score, 31% (13/42) were favourable, 57% (24/42) were intermediate and 12% (5/42) had poor risk disease at diagnosis (**Fig. 6**). There was no statistical difference in the patient distribution when comparing the MSKCC and IMDC scores ($p > 0.99$).

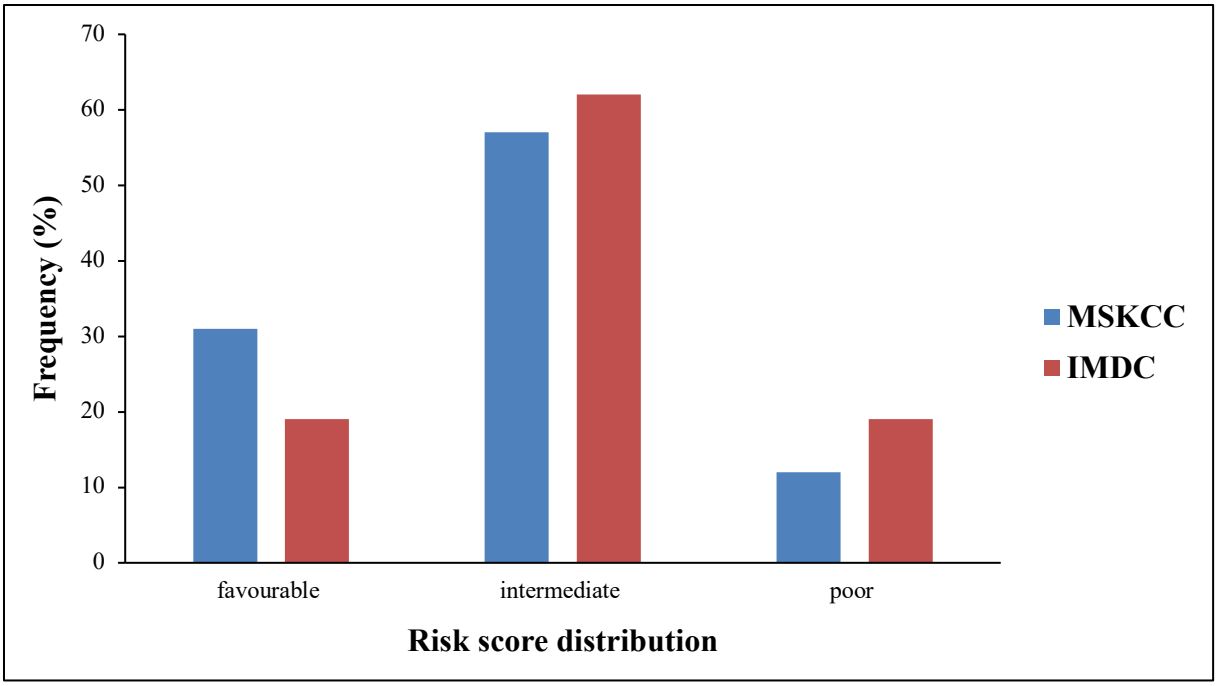


Figure 6 *– Distribution of the MSKCC and IMDC risk groups in patients with metastatic type 2, papRCC.*

The tumour stage of the primary renal cell carcinoma was T1 in 36% (15/42), T2 in 12% (5/42), T3 in 36% (15/42) and 16% (7/42) of patients had T4 disease at the time of first diagnosis, respectively **(Fig. 7).**

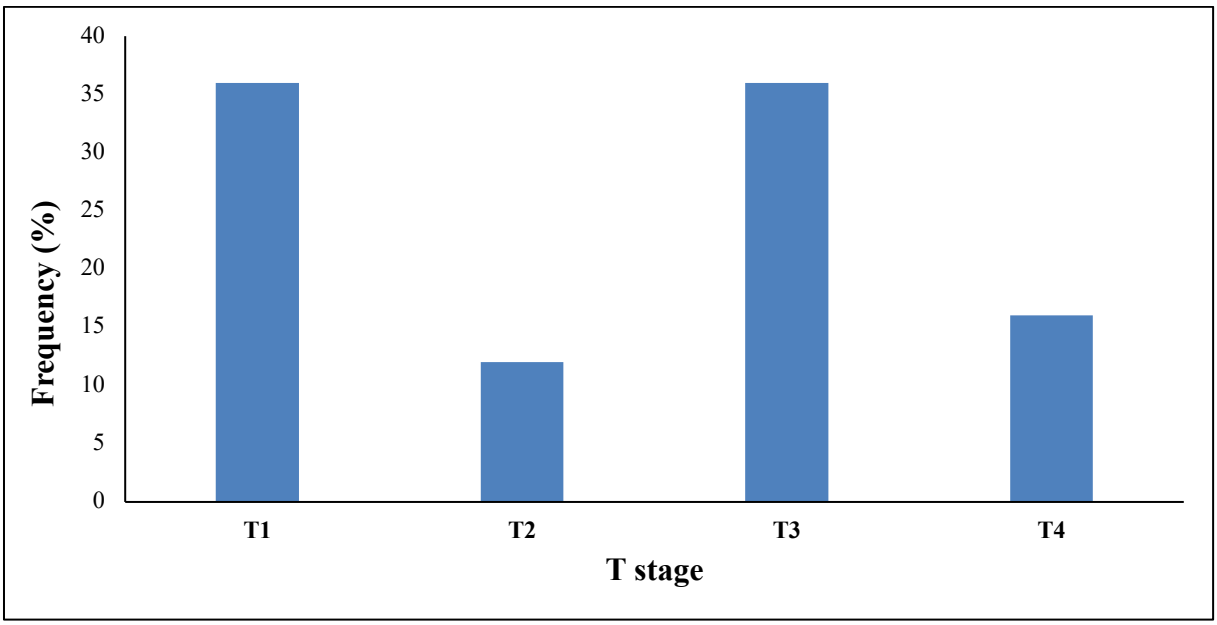


Figure 7 *– Tumour stage of the primary RCC at first diagnosis in patients with type 2, papRCC.*

The majority of the patients (71%, 30/42) had high grade (Fuhrman grade 3) disease while the remaining 29% (12/42) had low grade (Fuhrman grade 2) disease at first presentation **(Fig. 8).**

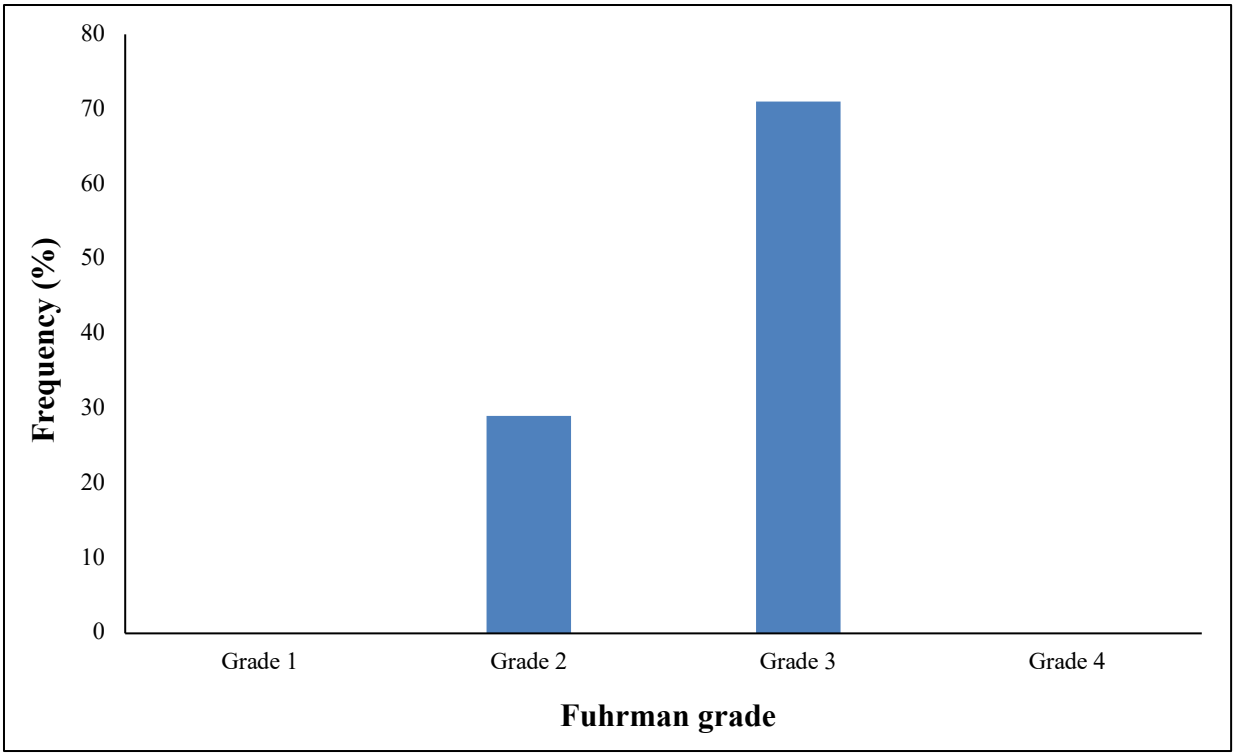


Figure 8 *- Distribution of Fuhrman grade of the primary RCC.*

There was no statistically significant association between the clinical stage of the primary tumour and Fuhrman grade (p= 0.1225) (**Fig. 9).**

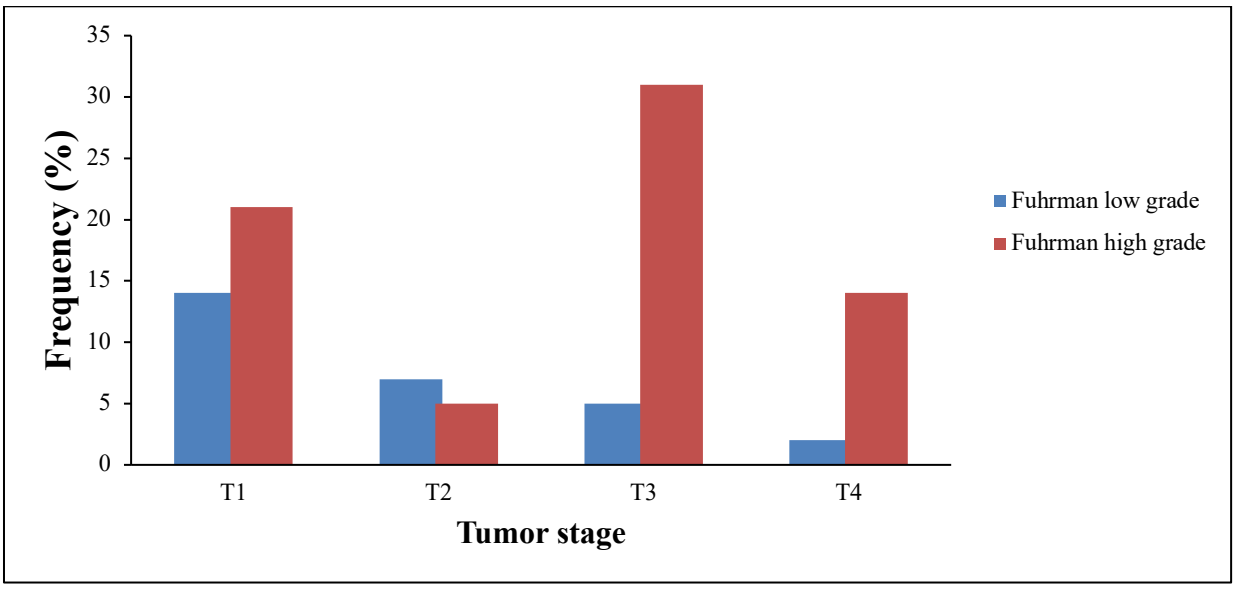


Figure 9 *- Association between tumour stage and Fuhrman grade of the primary tumour.*

4.2. Characteristics of metastatic disease

From the 42 patients, 50% (21/42) presented with upfront metastatic disease whilst the remaining patients were diagnosed with organ-confined disease at initial presentation. These patients underwent surgical therapy i.e., partial, or radical nephrectomy with curative intent and developed metastatic disease subsequently. From these, 43% (9/21) developed distant

metastasis within 12 months post-surgery. The median DFS was 14.9 months (95% CI, 2.5 – 27.3) (**Fig. 10).**

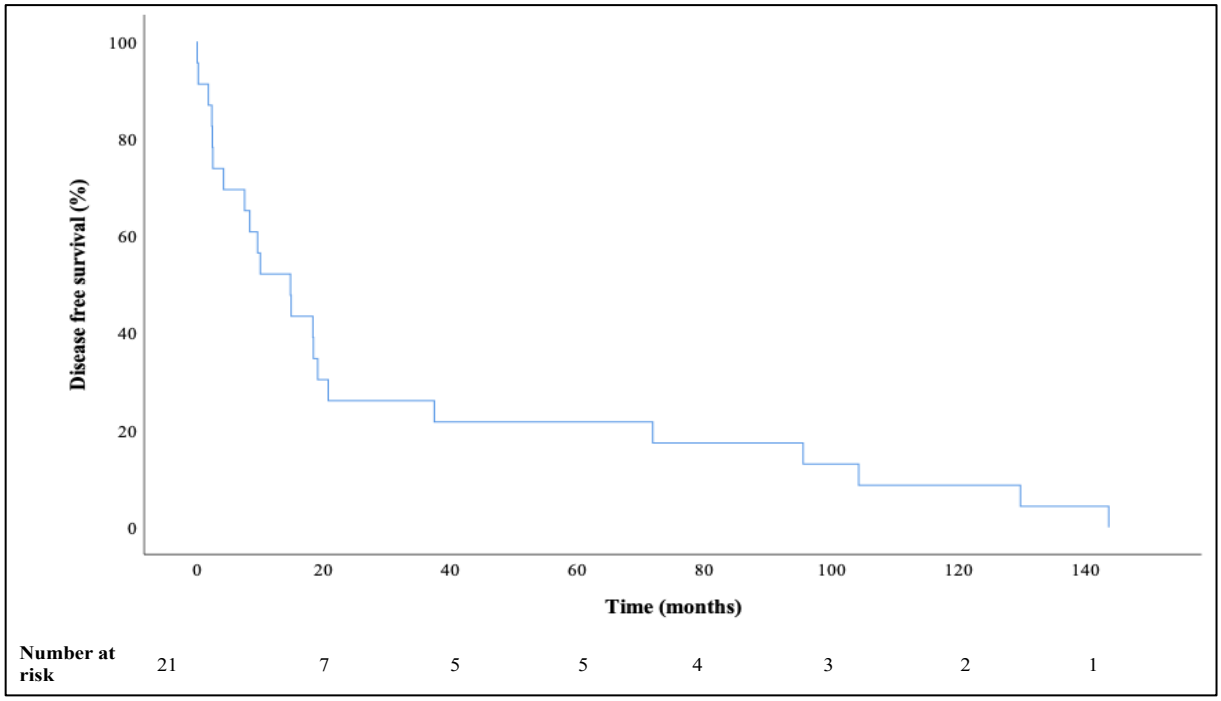


Figure 10 *- Kaplan–Meier estimates of disease-free survival of patients presenting with initially organ-confined disease.*

The most common sites of metastatic disease were lymph node (67%, 28/42), lung (36%, 15/42), liver (24%, 10/42) and bone (19% 8/42). Furthermore, 10% (4/42) of patients had cerebral metastasis **(Fig. 11).**

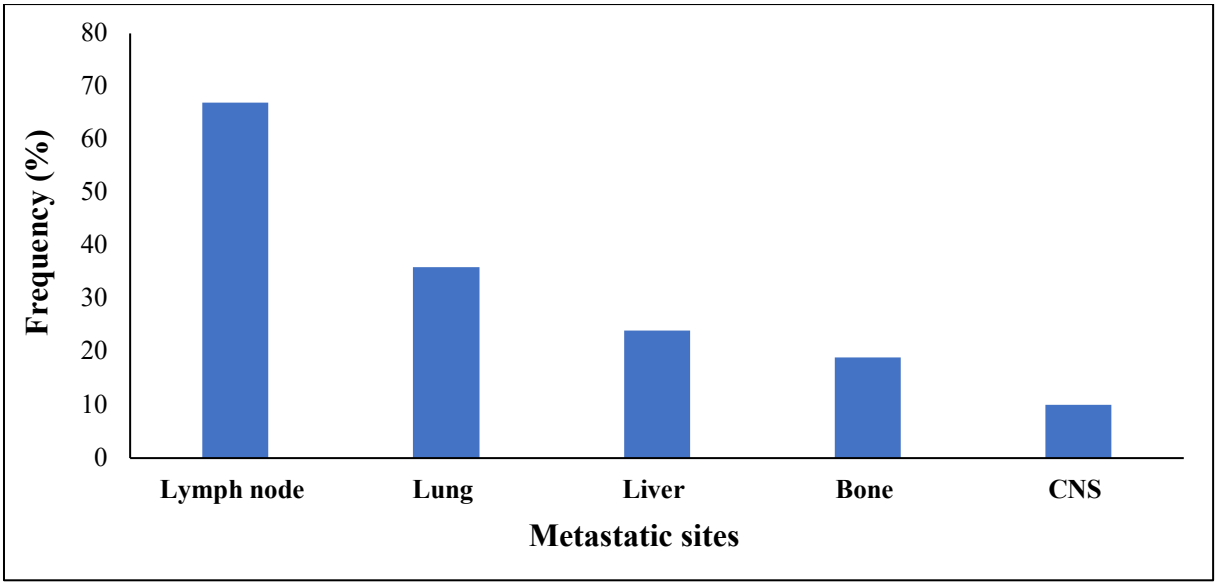


Figure 11 *- Sites of metastatic disease at first diagnosis.*

Presentation with upfront metastatic disease at first diagnosis was associated with various clinicopathological factors including poor ECOG performance status (p=0.021), higher

MSKCC risk (p=0.004) and higher IMDC score (p=0.013), no previous nephrectomy (p=0.045) and higher tumour stage (p=0.012) **(Table 5).**

Table 5. Correlation between upfront metastatic disease and baseline clinico-pathological characteristics

Characteristics	**Development of metastatic disease**		**p-value**
	Subsequently (M0) N. (%)	Upfront (M1) N. (%)	
Age			
<65 years	13 (65)	15 (68)	
≥65 years	7 (35)	7 (32)	0.827
Gender			
Male	13 (65)	15 (68)	
Female	7 (35)	7 (32)	0.827
ECOG PS			
0	11 (55)	4 (18)	
1	9 (45)	15 (68)	
2	0	3 (14)	**0.021**
MSKCC risk score			
favourable	3 (15)	5 (23)	
intermediate	9 (45)	17 (77)	
poor	8 (40)	0	**0.004**
IMDC risk score			
favourable	3 (15)	10 (45)	
intermediate	12 (60)	12 (55)	
poor	5 (25)	0	**0.013**
Previous nephrectomy			
yes	20 (100)	18 (82)	
no	0	4 (18)	**0.045**
Tumour stage			
T1	11 (55)	4 (18)	
T2	3 (15)	2 (9)	
T3	6 (30)	9 (41)	
T4	0	7 (32)	**0.012**
Fuhrman Grade			
2	8 (40)	4 (18)	
3	12 (60)	18 (82)	0.118

ECOG: Eastern Cooperative Oncology Group, PS: performance status, MSKCC: Memorial Sloan-Kettering Cancer Centre, IMDC: International Metastatic RCC Database Consortium

4.3. Surgical treatment

Most patients (91%, 38/42) underwent prior surgical treatment (nephrectomy). Based on tumour size and anatomical localization of the tumour, patients underwent either partial nephrectomy (40%, 15/42) or radical nephrectomy (60%, 23/42). All patients who presented with organ confined disease at first diagnosis (50%, 21/42) underwent surgical treatment. From patients with upfront metastatic disease, 81% (17/21) underwent cytoreductive treatment either with partial- (18%, 3/17) or with radical nephrectomy (82%, 14/17). Four (9%, 4/42) patients

didn't undergo surgery due to the size of the primary tumour (4/4) extensive metastatic disease (2/4) or concomitant cerebral metastasis (1/4). From these, two patients had MSKCC poor risk and three had IMDC poor risk disease. The median OS in patients who underwent CN was 9.8 months (95%CI, 1.8-17.8) vs 7.7 months (95%CI, 0.0-16.4) in those who did not **(Fig. 12).** There was no statistically significant between the two groups of patients (p=0.777).

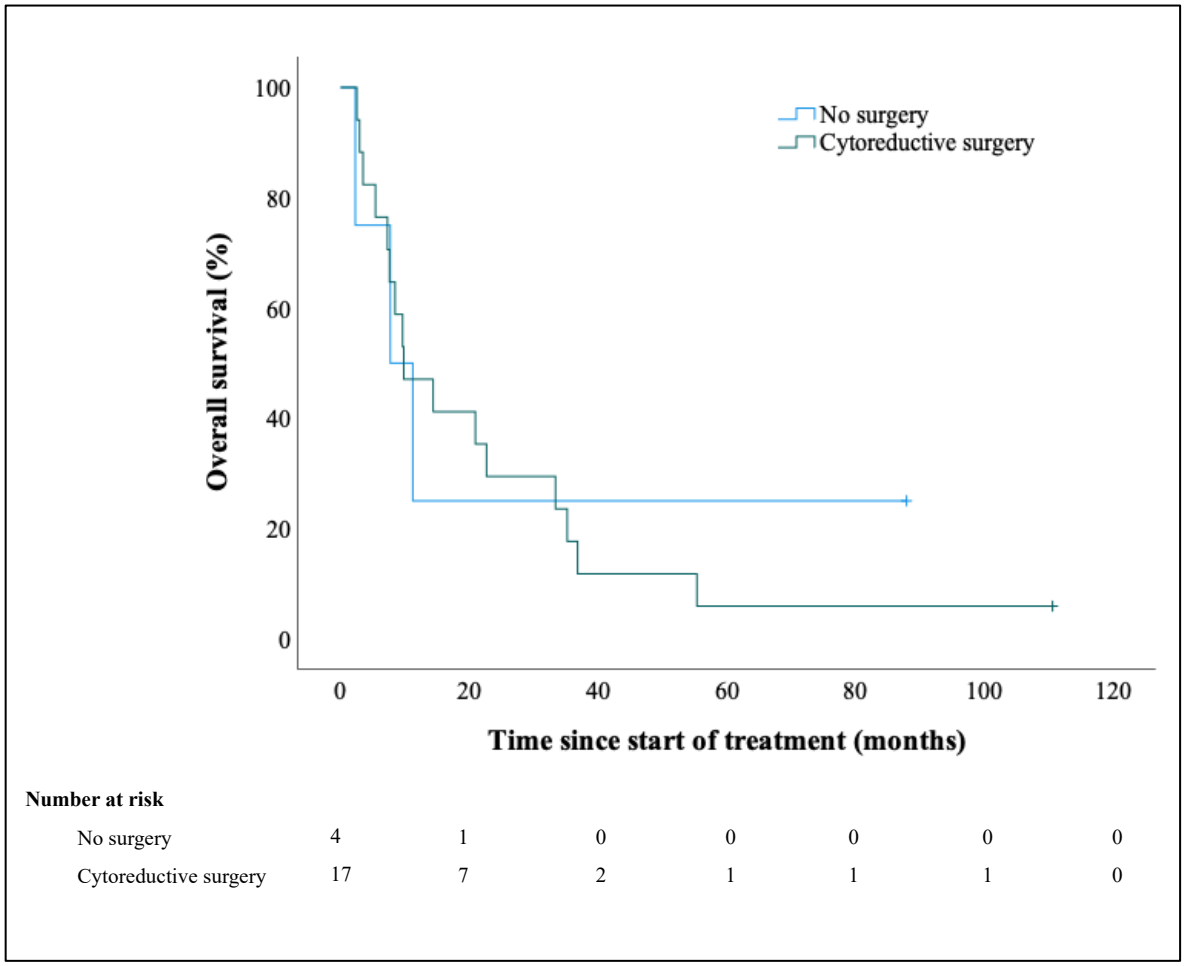


***Figure 12** - Kaplan–Meier estimates of overall survival stratified by CN. Tick marks represent data censored at the last time the patient was known to be alive at the data cut -off.*

There was no association between the type of surgery (partial vs radical nephrectomy) and upfront metastatic disease (p=0.162), ECOG performance status (p=0.975), MSKCC risk score (p=0.210), IMDC risk score (p=0.323). However, there was a significant association with the clinical stage of the primary tumour (p<0.001).

4.4. Systemic therapies

Between January 2005 and December 2015, 42 patients with previously untreated, metastatic, type 2, papRCC started systemic therapy. As of 9th of May 2016, the data cut-off date, 17% (7/42) of patients were alive and continued active treatment. At a median follow up of 71 months (95%CI, 24-118), 83% (35/42) of patients died, all due to progression of disease.

All patients received first line systemic therapy, however after progression, only 48% (20/42) received second line, 21% (9/42) third line and 5% (2/42) received fourth line therapies (**Fig. 13**).

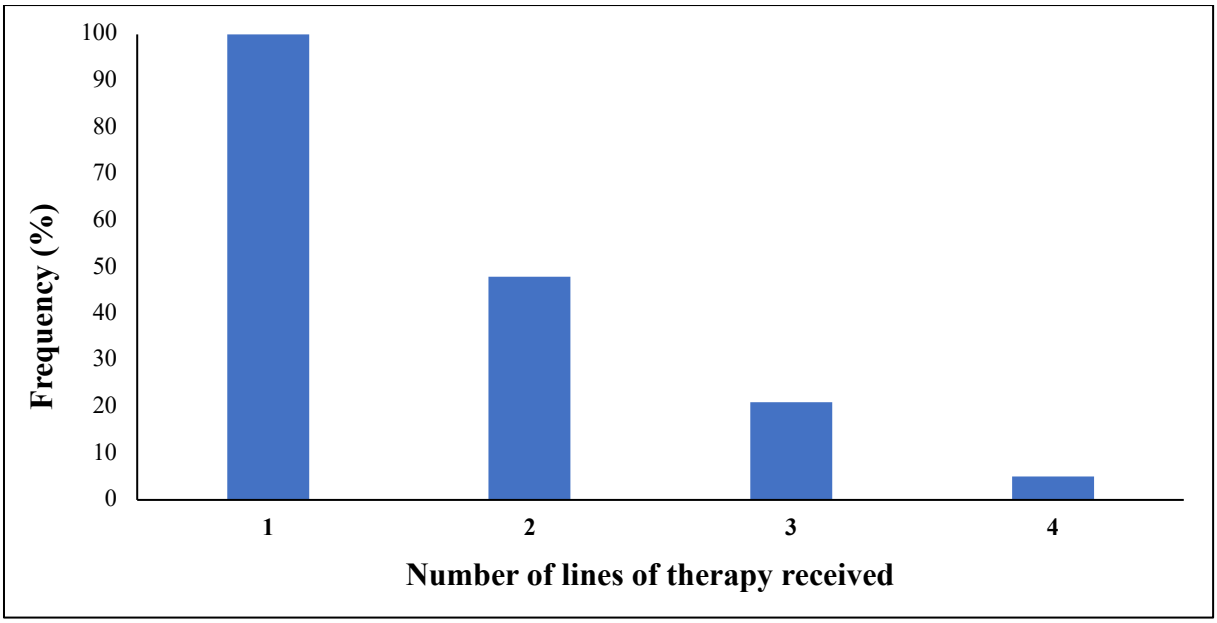


Figure 13 *- Number of therapy lines received by patients with metastatic, type 2, papRCC.*

The median OS was 10.5 months (95%CI, 5.4 – 15.7) **(Fig. 14).** The percentage of patients who were alive at 1-, 2- and 5 years were 41%, 31% and 5%, respectively.

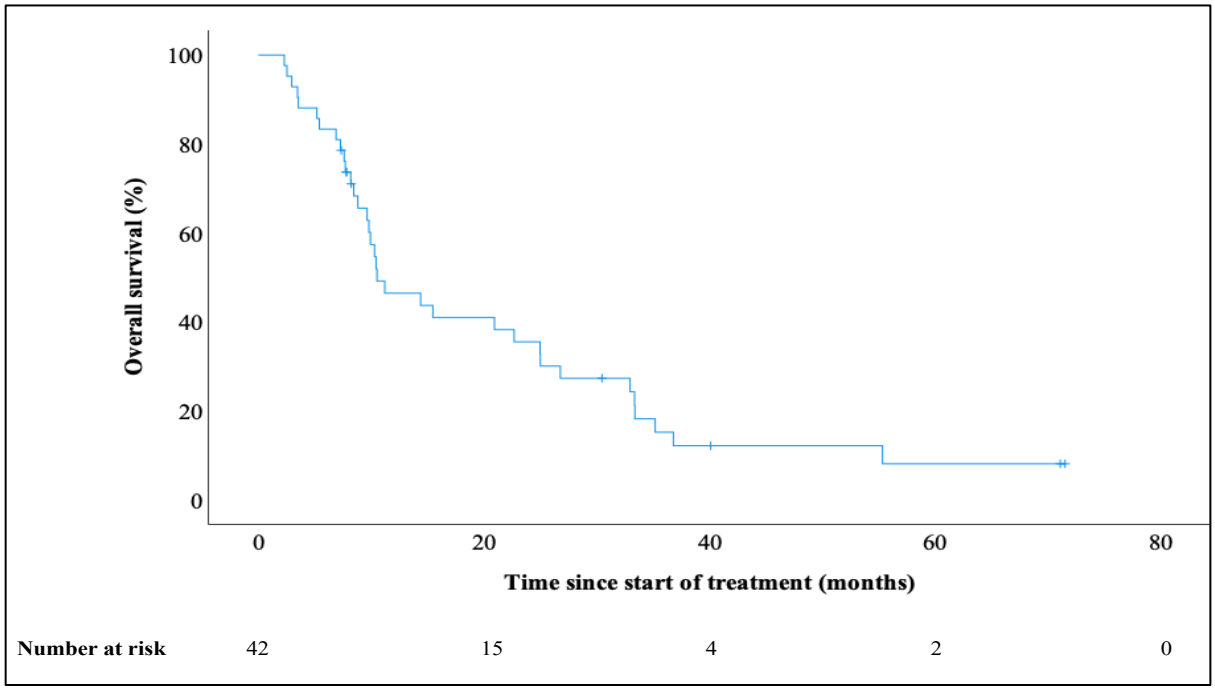


Figure 14 *- Kaplan–Meier estimates of OS. Tick marks represent data censored at the last time the patient was known to be alive at the data cut -off.*

4.4.1. First line therapy

All patients received first line targeted therapy according to the current German and international RCC guidelines at the time of starting treatment. First line therapy agents included VEGF- and mTOR inhibitors. The most used first line agent was sunitinib in 74% (31/42) of patients. Furthermore, 12% (5/42) received sorafenib and 10% (4/42) received temsirolimus. One patient (2%) had everolimus and one (2%) other was treated with first line pazopanib **(Fig. 15).**

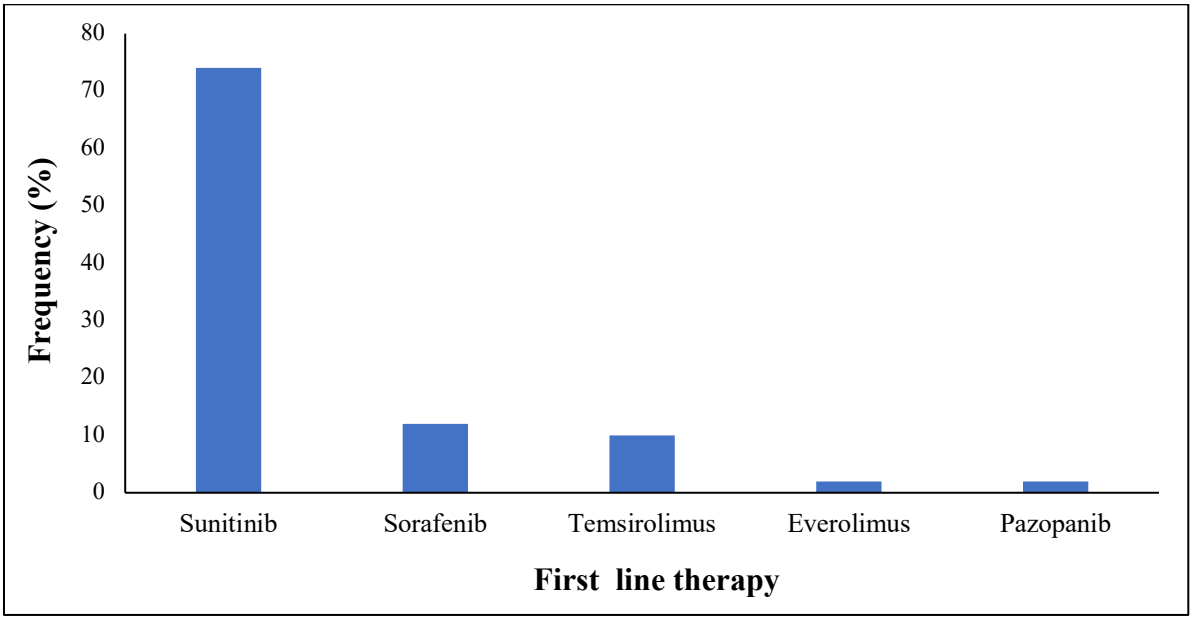


Figure 15 *- Frequency of first line therapy agents used.*

The ORR of the entire cohort was 19% (8/42). Patients receiving sunitinib had an ORR of 26% (8/31) with 10% (3/31) of patients achieving complete response. There were no responders in the non-sunitinib treated patients **(Fig. 16).**

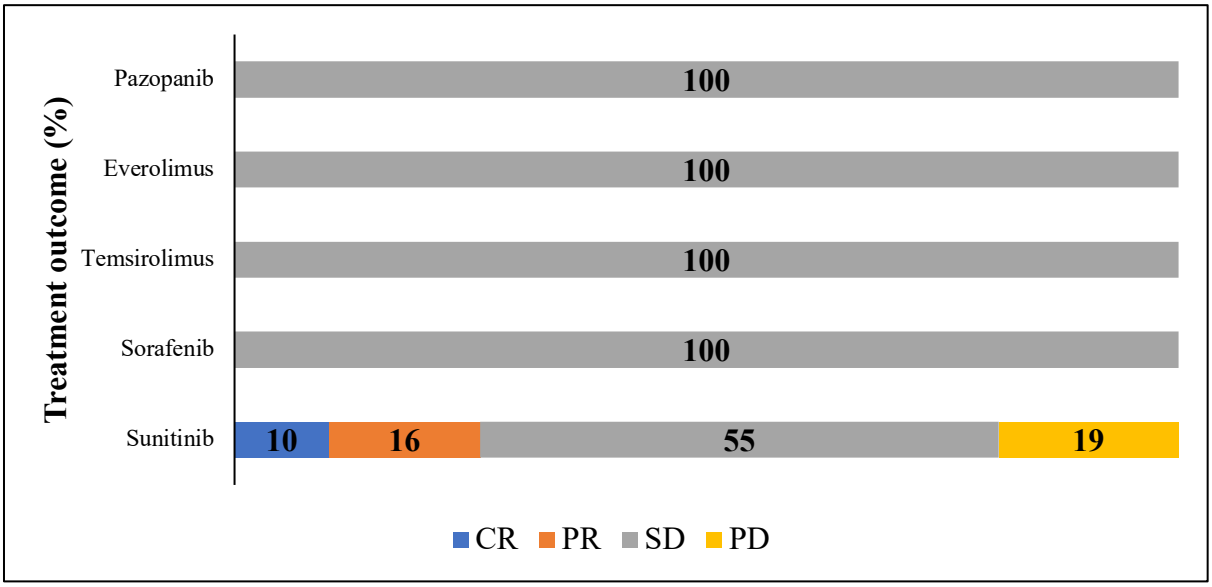
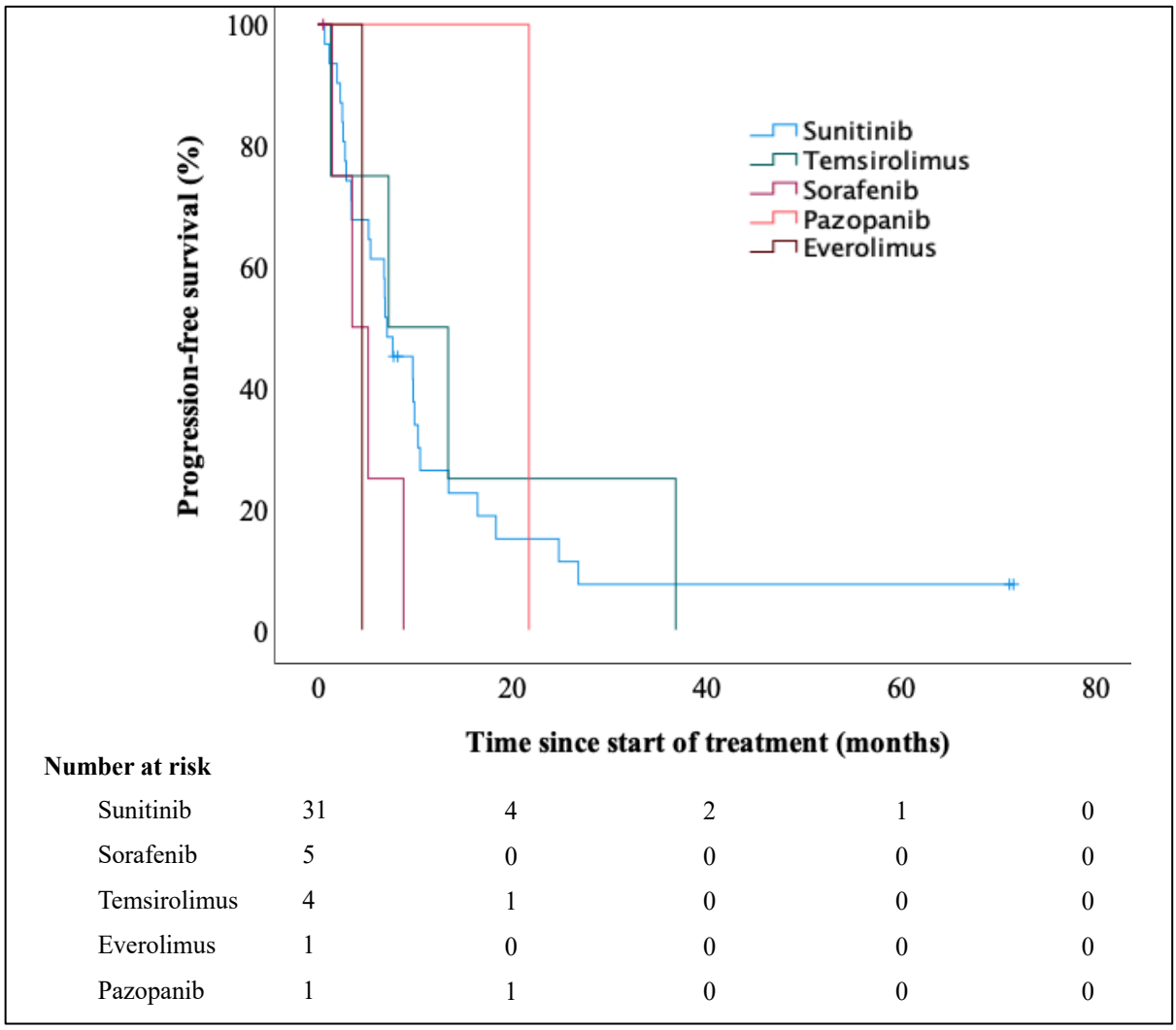


Figure 16 *– Treatment outcomes of patients receiving first line targeted therapy agents; CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease*

The median PFS was 7.1 months (95%CI, 6.0 – 8.2) in the overall cohort. The median PFS for patients treated with first line sunitinib, temsirolimus and sorafenib were 7.1 months (95%CI, 4.0 – 10.2), 7.2 months (95%CI, 0.1 – 19.1) and 3.5 months (95%CI, 0.1 – 7.1), respectively **(Fig. 17).** There were no statistically significant differences between the different treatment groups and outcomes (p=0.348). The median PFS was not assessed for patients receiving pazopanib and everolimus due to low patient numbers (pazopanib: n=1, everolimus: n=1). Progression-free survival individually for these two patients were 21.7 months (pazopanib) and 4.6 months (everolimus).

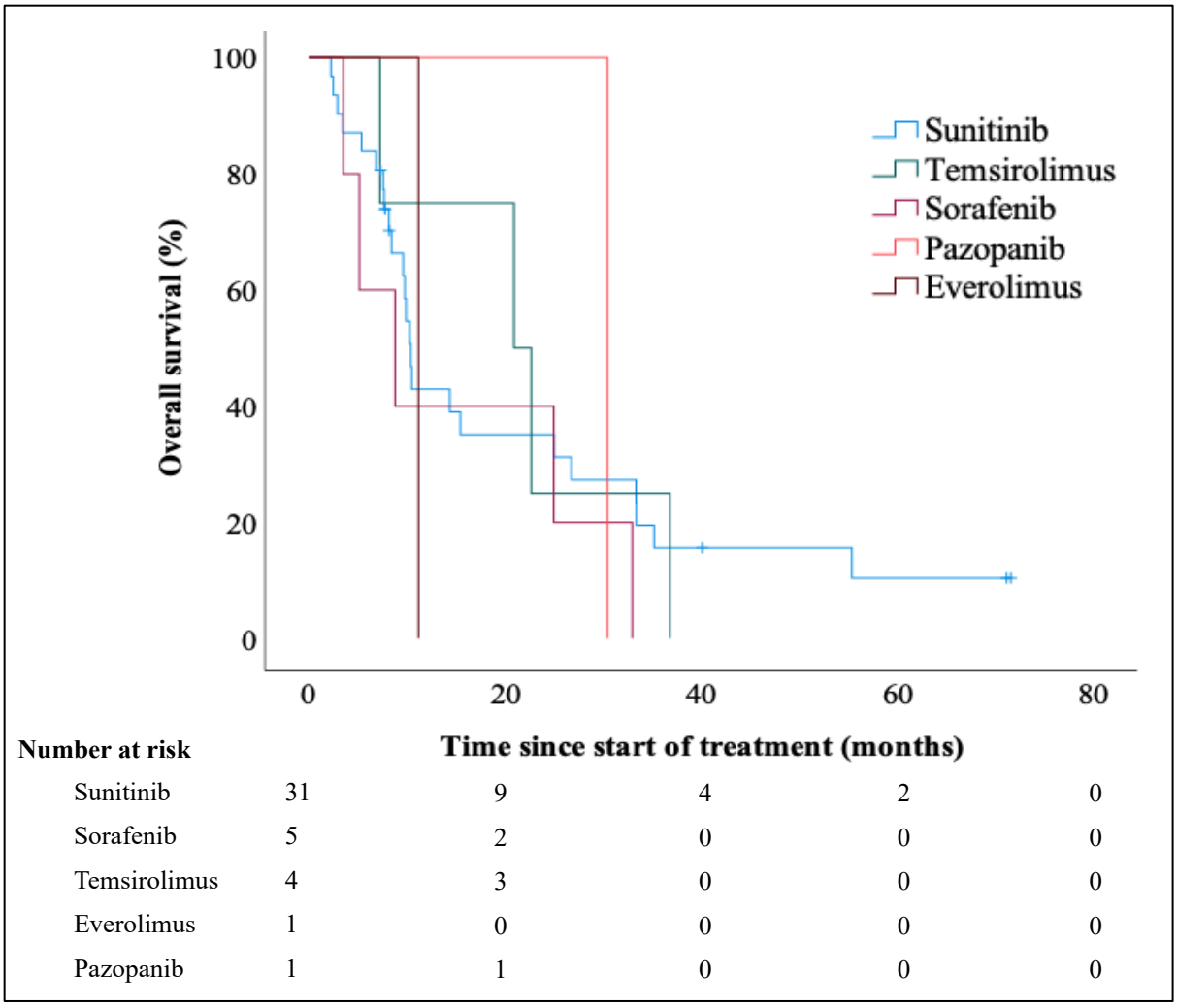


Number at risk

Sunitinib	31	4	2	1	0
Sorafenib	5	0	0	0	0
Temsirolimus	4	1	0	0	0
Everolimus	1	0	0	0	0
Pazopanib	1	1	0	0	0

***Figure 17** - Kaplan–Meier estimates of progression-free survival according to first line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive and free from disease progression (at the time of data cut-off).*

The median OS for patients receiving first line sunitinib, temsirolimus and sorafenib was 10.4 months (95%CI, 9.6 – 11.3), 21.0 months (95%CI, 5.9 – 36.1) and 8.8 months (95%CI, 1.0 – 16.6), respectively **(Fig. 18).** There were no statistically significant differences between the different treatment groups and OS (p=0.874). Median OS was not calculated for patients who received first line pazopanib (n=1) and everolimus (n=1).



Number at risk					
Sunitinib	31	9	4	2	0
Sorafenib	5	2	0	0	0
Temsirolimus	4	3	0	0	0
Everolimus	1	0	0	0	0
Pazopanib	1	1	0	0	0

Figure 18 *- Kaplan–Meier estimates of OS according to first line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive (at the time of data cut-off).*

4.4.2. Second line therapy

From the 42 patients initially included in our cohort, only 48% (20/42) went on to receive subsequent therapies, after disease progression. The most common second line agents were sorafenib (35%, 7/20) and axitinib (30%, 6/20). In addition, 20% (4/20) of patients received second line sunitinib, 10% (2/20) received everolimus and one patient (5%) was treated with pazopanib **(Fig. 19).**

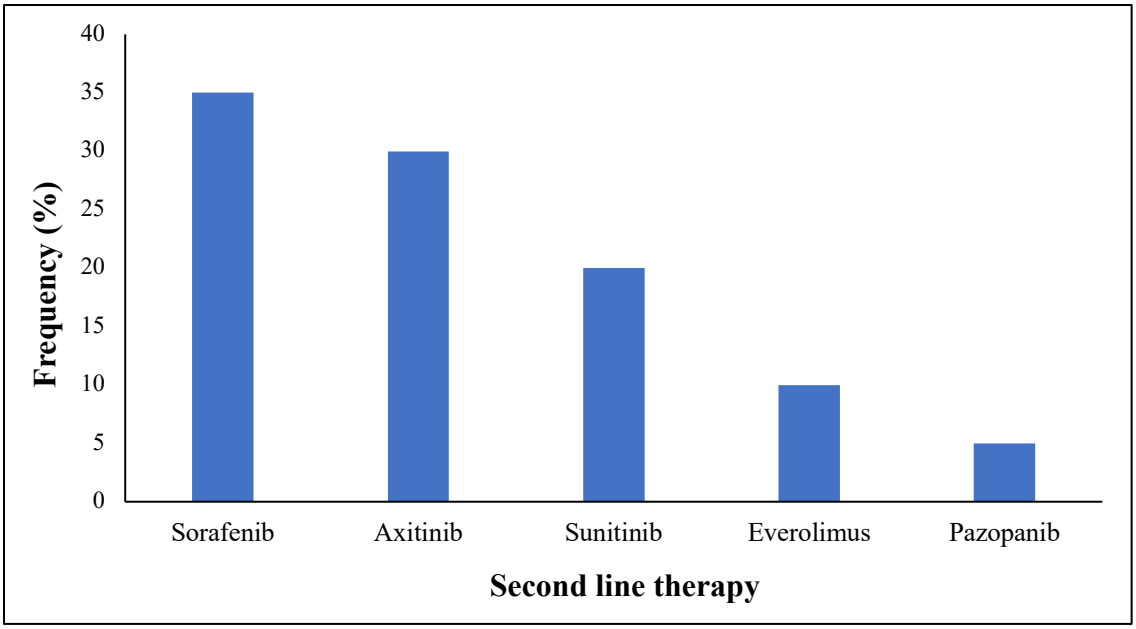


Figure 19 *– Type and frequency of second line therapy agents used after progression on disease.*

There were no responders amongst the patients receiving second line therapy. The best outcome was stable disease in 70% (14/20) of patients and progression of disease in 30% (6/20) of patients. Amongst patients treated with sunitinib, all patients (100% 4/4) achieved stable disease. Patient receiving second line sorafenib, 43% (3/7) had stable disease and 57% (4/7) had progression of disease as best response. In the axitinib treated patients, 83% (5/6) achieved stable disease and 1 patient (17%) had progressed. Two patients received everolimus. One of them had stable disease while the other had progressed on therapy. Lastly, one patient received second line pazopanib and achieved stable disease as best response to therapy **(Fig. 20).**

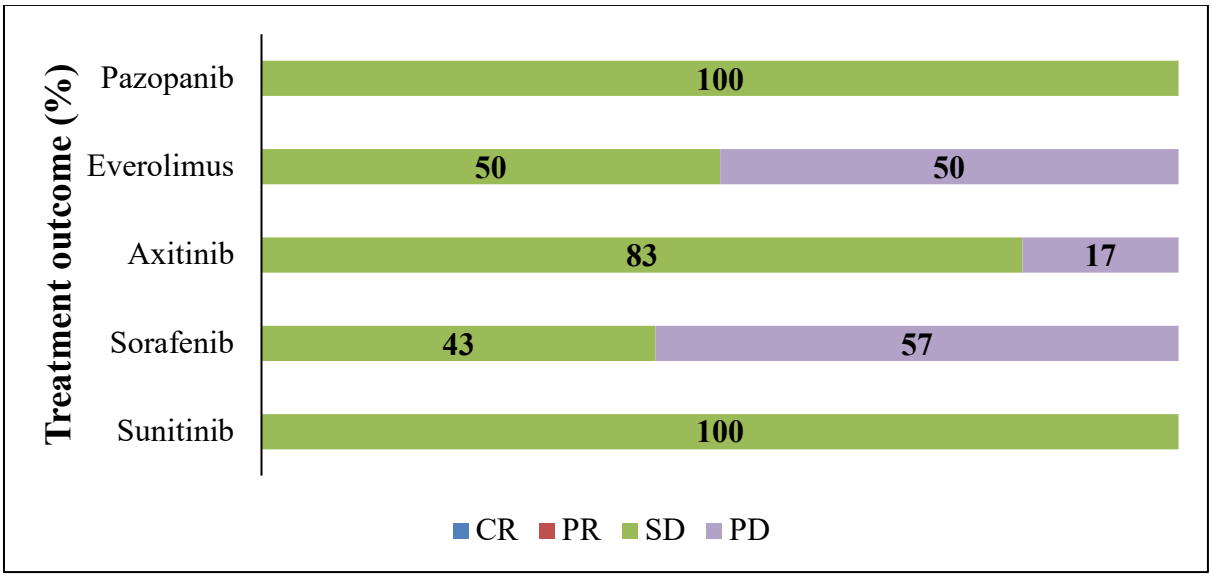
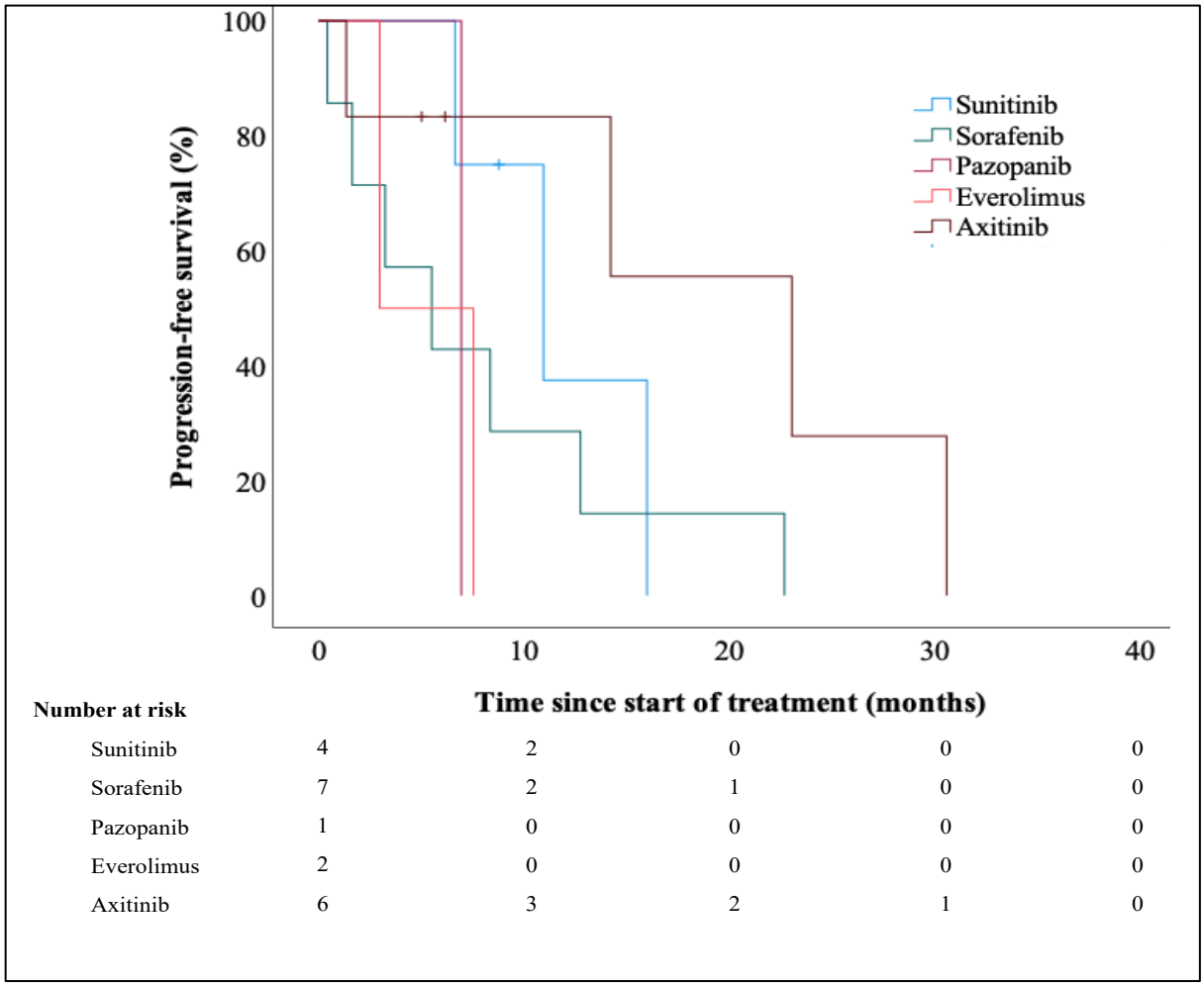


Figure 20 *- Treatment outcomes of patients receiving second line targeted therapy agents; CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease*

The median PFS was 8.4 months (95%CI, 3.3 – 13.4) in the overall cohort. The median PFS for patients treated with second line sorafenib, axitinib and sunitinib was 5.5 months (95%CI, 0.1 – 11.3), 23.0 months (95%CI, 8.6 – 37.5) and 11.0 months (95%CI, 4.5 – 17.4), respectively. There were no statistically significant differences between the different treatment groups and outcomes (p=0.173). Median PFS was not assessed for patients receiving pazopanib and everolimus due to low patient numbers (pazopanib: n=1, everolimus: n=2). Progression-free survival specifically for the single patient treated with second line pazopanib was 7.0 months. Progression-free survival for the two patients on second line everolimus was 3.0 and 7.5 months **(Fig. 21).**



Number at risk					
Sunitinib	4	2	0	0	0
Sorafenib	7	2	1	0	0
Pazopanib	1	0	0	0	0
Everolimus	2	0	0	0	0
Axitinib	6	3	2	1	0

Figure 21 *- Kaplan–Meier estimates of PFS according to second line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive and free from disease progression (at the time of data cut-off).*

The median OS for patients starting on second line therapy (48%, 20/42) was 8.8 months (95%CI, 4.2 – 13.4). The median OS for patients receiving second line sorafenib, axitinib and sunitinib was 8.4 months (95%CI, 4.7 – 12.0), 23.6 months (95%CI, 8.0 – 39.2), 8.8 months (95%CI, 0.1 – 23.2), respectively. There were no statistically significant differences between the different treatment groups and OS (p=0.354). Median OS was not calculated for patients receiving second line pazopanib and everolimus due to low patient numbers **(Fig. 22).**

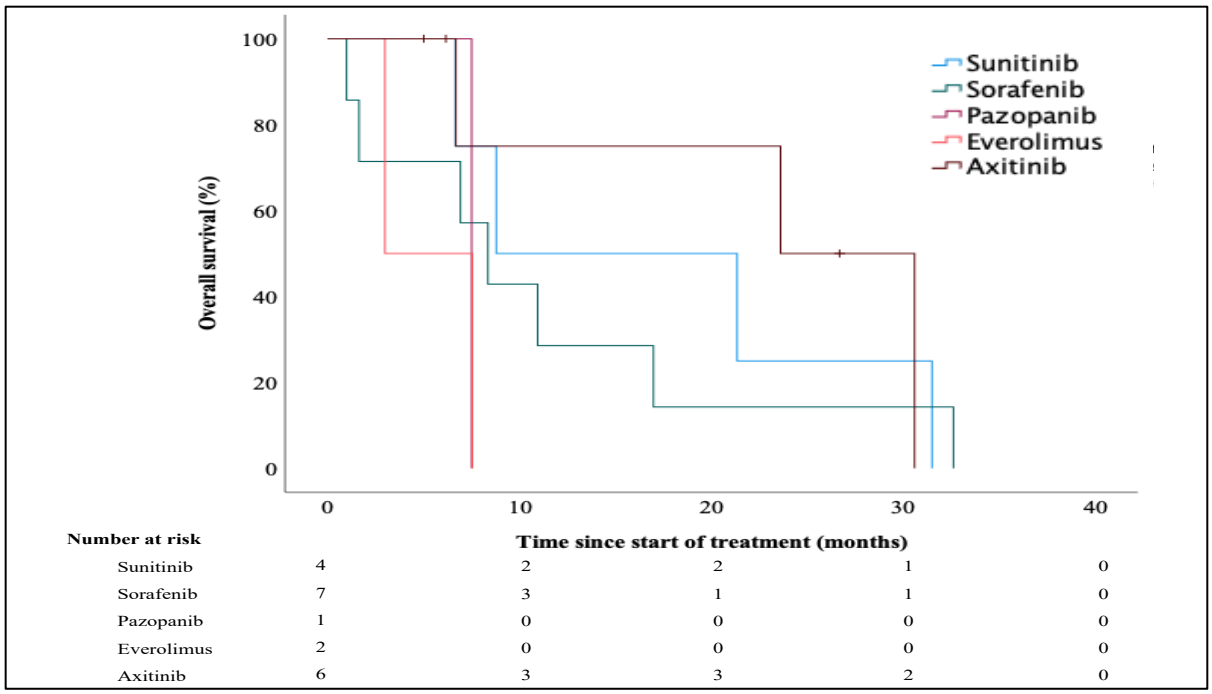


Figure 22 *- Kaplan–Meier estimates of OS according to second line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive (at the time of data cut-off).*

4.4.3. Third line therapy

From those on second line treatment, only 45% (9/20) went on to receive third line treatment. This represents only 21% (9/42) of the initial patient cohort. The most frequently administered therapy in the third line setting was everolimus (44%, 4/9), followed by axitinib (22%, 2/9). Additional three patients received nivolumab (n=1), pazopanib (n=1) and sorafenib (n=1) as well **(Fig. 23).**

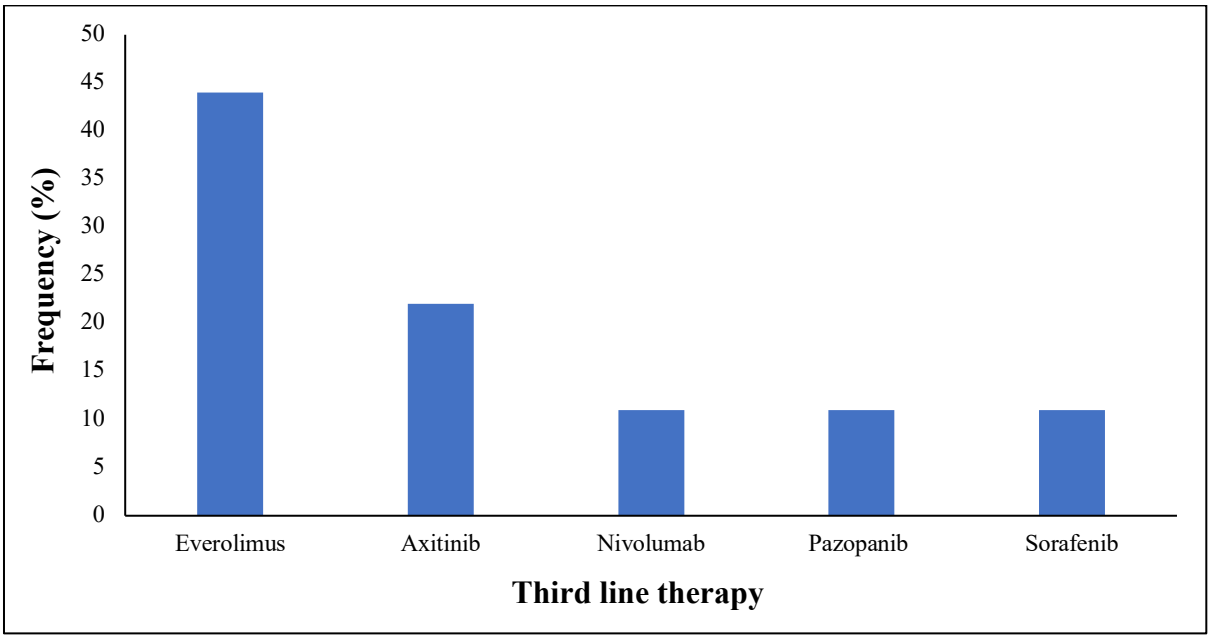


Figure 23 *– Type and frequency of third line therapy agents used after progression of disease.*

Similar to the second line, in the third line setting there were no patients achieving partial or complete responses. Stable disease was seen in 78% (7/9) of patients and upfront progression in 22% (2/9) of patients. Amongst patients receiving everolimus, 75% (3/4) had stable disease as their best response to therapy and one patient demonstrated upfront progression of disease. All patients in the axitinib (n=2), nivolumab (n=1) and pazopanib (n=1) group had stable disease. One patient who received sorafenib had disease progression **(Fig. 24).**

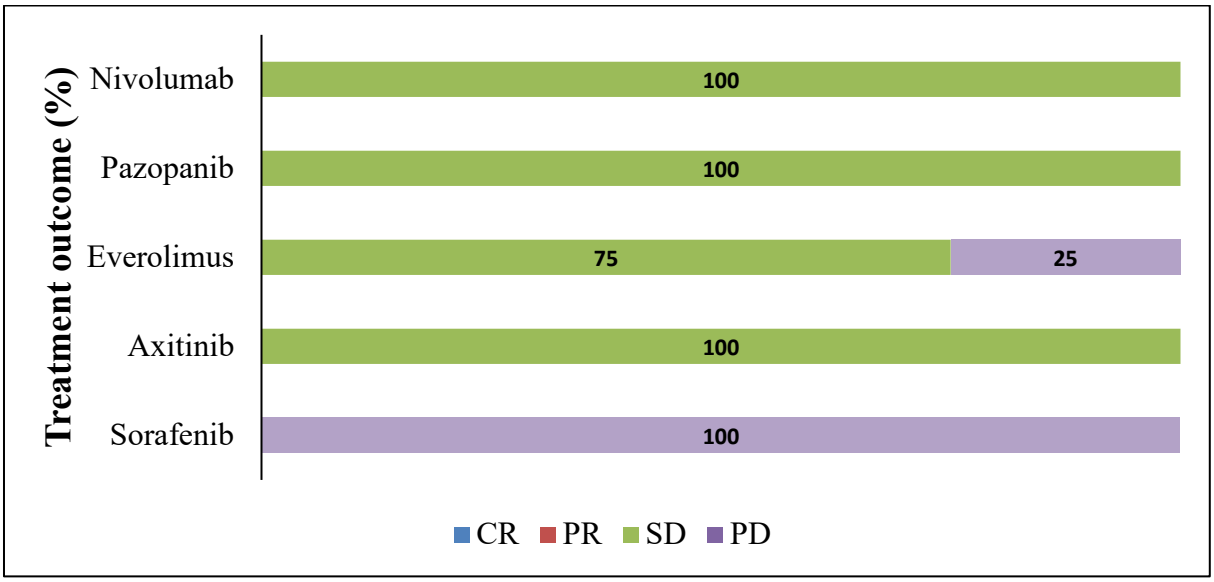


Figure 24 *- Treatment outcomes of patients receiving third line targeted therapy agents; CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease*

The median PFS amongst patient receiving third line therapy was 5.4 months (95%CI, 0.5 – 10.5) in the overall cohort. The median PFS for patients treated with third line everolimus was 4.2 months (95%CI, 2.5 – 6.0). Median PFS was not assessed for patients receiving sorafenib (n=1), pazopanib (n=1), nivolumab (n=1) and axitinib (n=2) due to low patient numbers **(Fig. 25).**

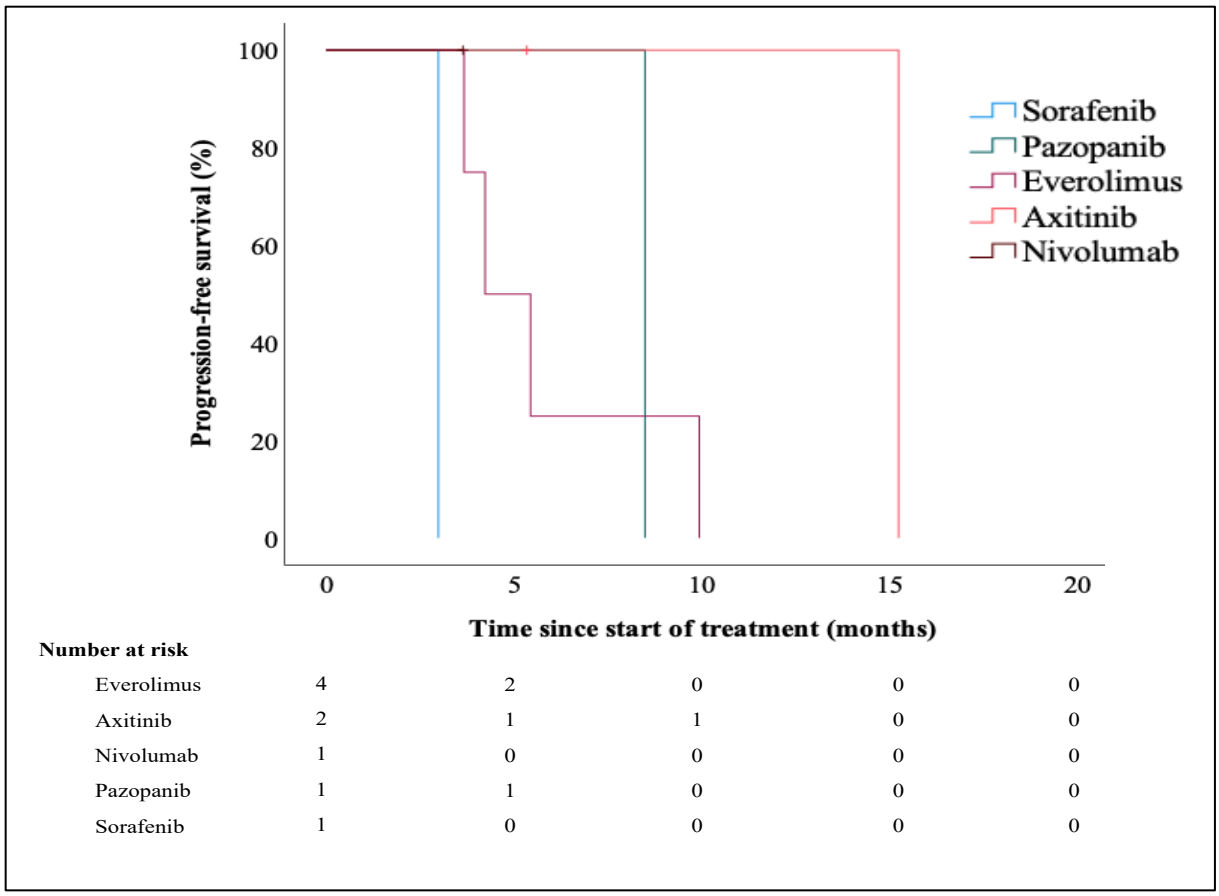


Figure 25 *- Kaplan–Meier estimates of PFS according to third line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive and free from disease progression (at the time of data cut-off).*

The median OS for patients who started on third line therapy (21%, 9/42) was 5.3 months (95%CI, 4.2 – 6.5). The median OS for patients receiving third line everolimus was 4.2 months (95%CI, 2.5 – 6.0). Median OS was not calculated for patients receiving third line sorafenib, pazopanib, nivolumab and axitinib due to low patient numbers **(Fig. 26).**

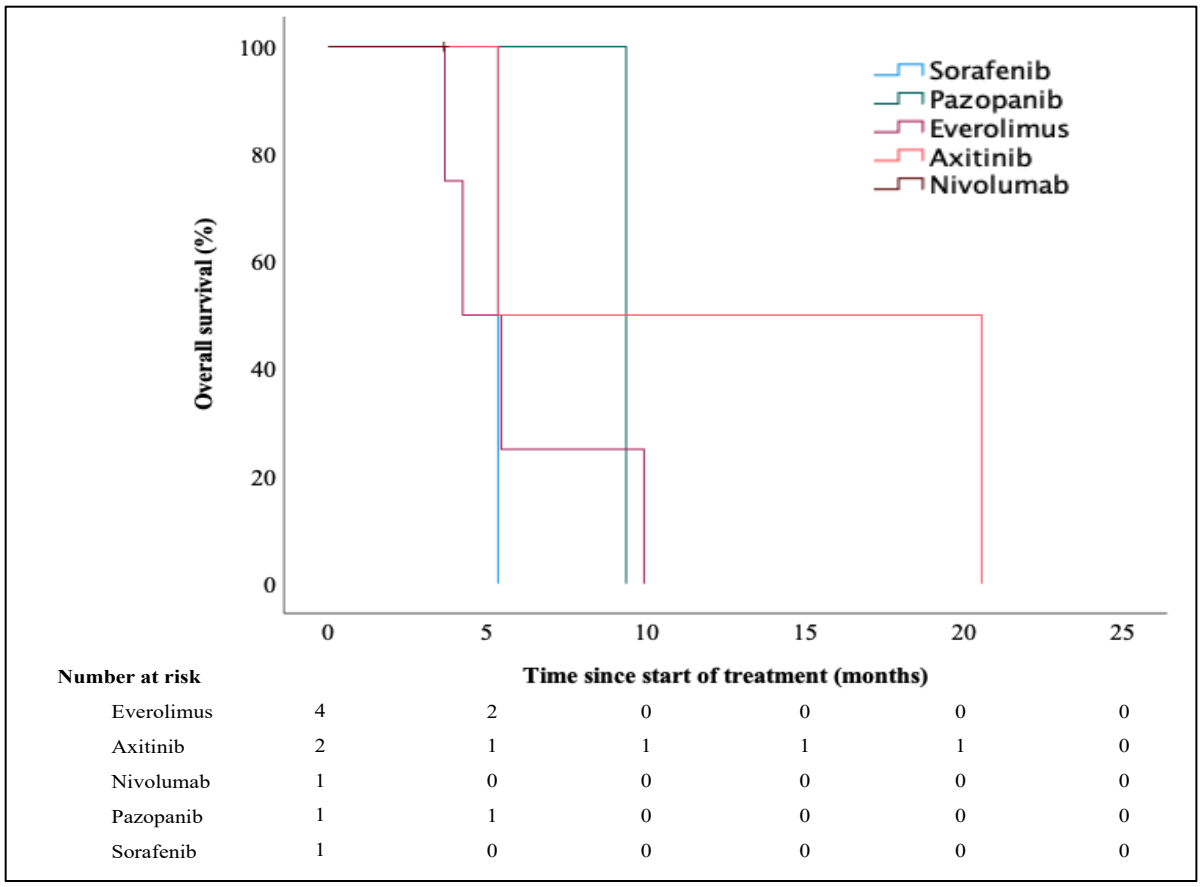


Figure 26 *- Kaplan–Meier estimates of OS according to third line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive (at the time of data cut-off).*

4.4.4. Fourth line therapy

From those on third line treatment, only two patients (22%, 2/9) received fourth line therapy. This represents only 5% (2/42) of the initial patient cohort. One patient received pazopanib and the other one was treated with nivolumab **(Fig. 27).**

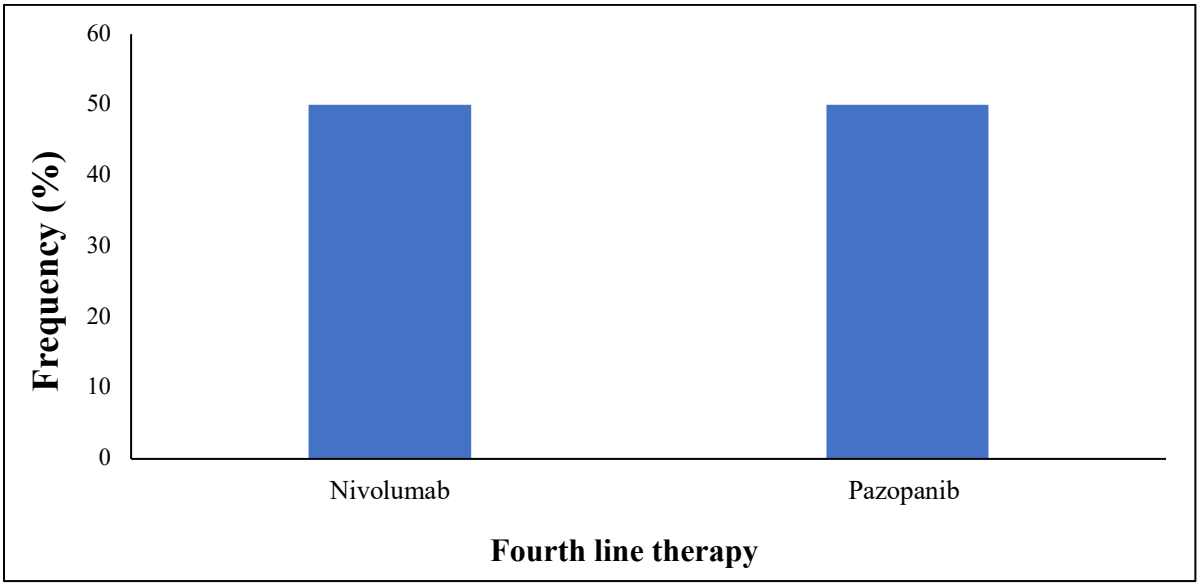


Figure 27 *– Type and frequency of fourth line therapy agents used after progression of disease.*

When looking at response to treatment, the patient receiving nivolumab demonstrated disease progression while the other one receiving pazopanib achieved stable disease as best response to therapy **(Fig. 28).**

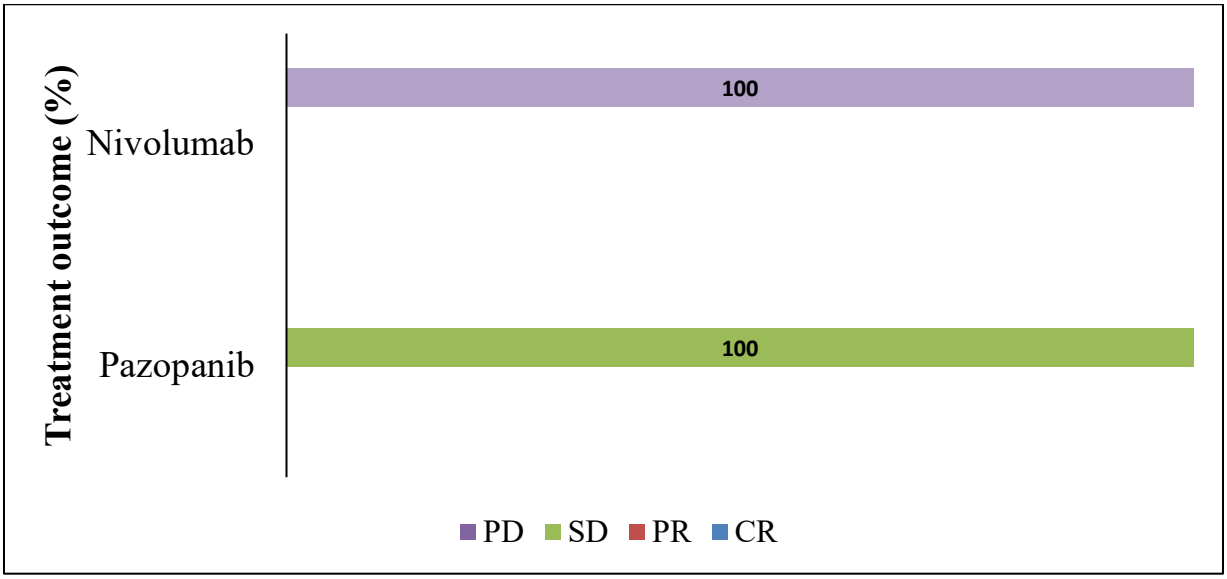


Figure 28 *- Treatment outcomes of patients receiving fourth line targeted therapy agents; CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease*

The PFS for the patient treated with nivolumab was 1.0 months and for the patient treated with pazopanib was 5.3 months **(Fig. 29).**

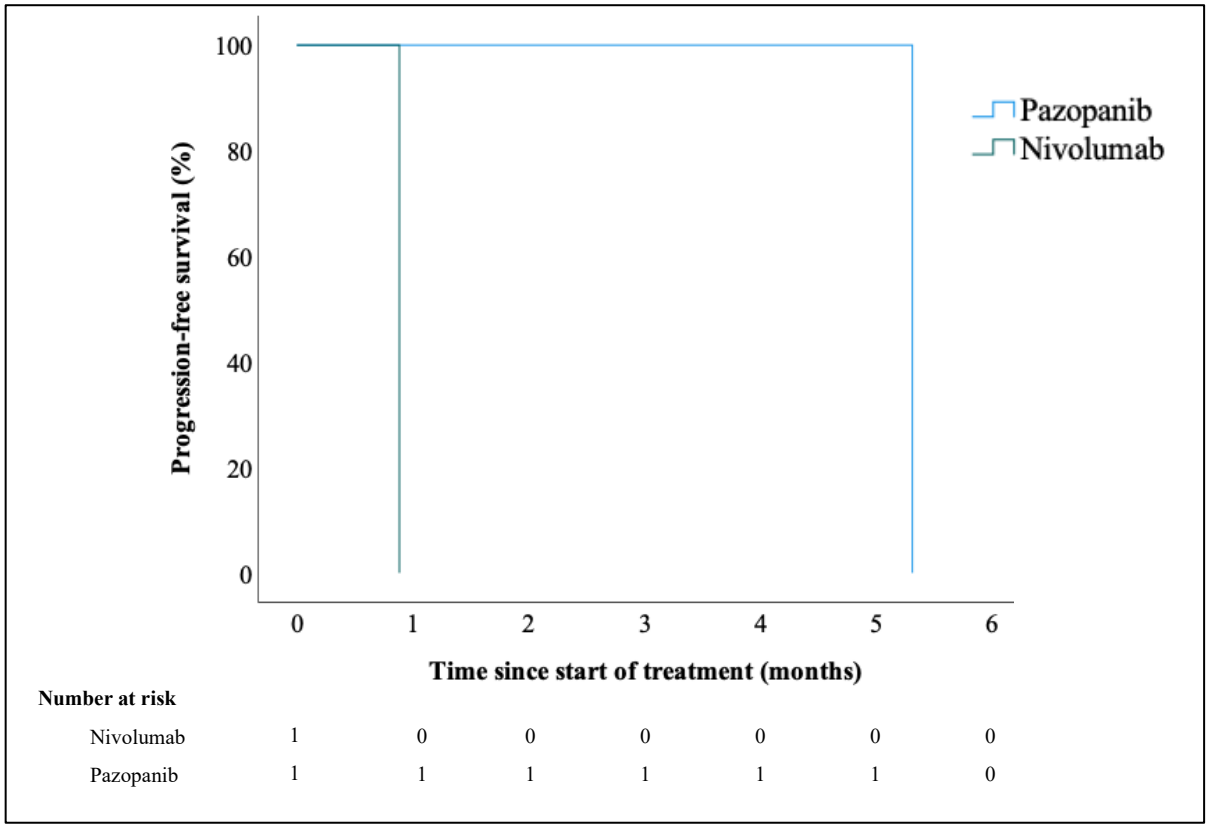


Figure 29 *- Kaplan–Meier estimates of PFS according to fourth line therapy agent. Tick marks represent data censored at the last time the patient was known to be alive and free from disease progression (at the time of data cut-off.*

4.4.5. Therapy sequencing

The Sankey diagram in **Figure 30** describes the treatment sequences of all patients in our cohort.

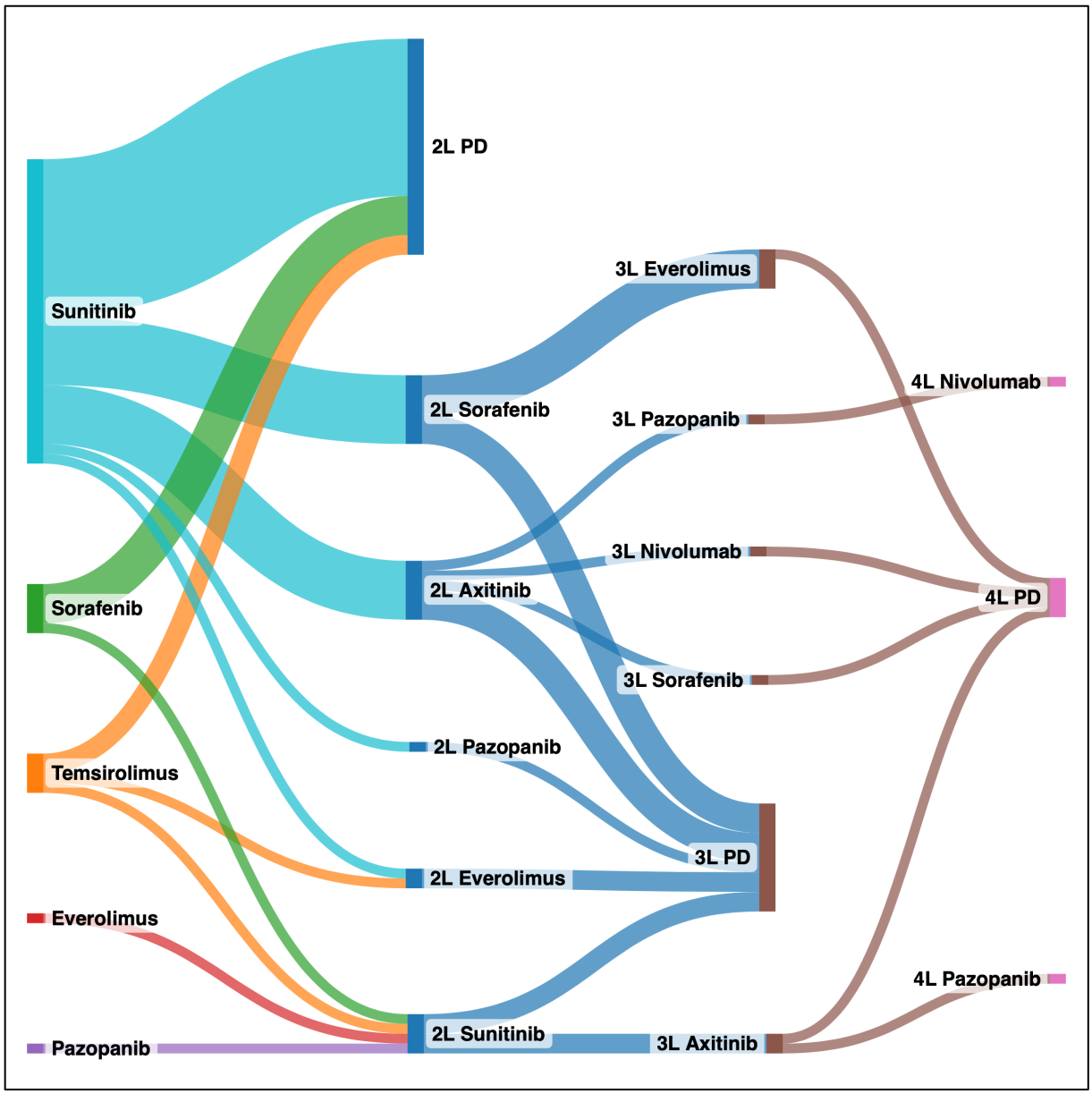
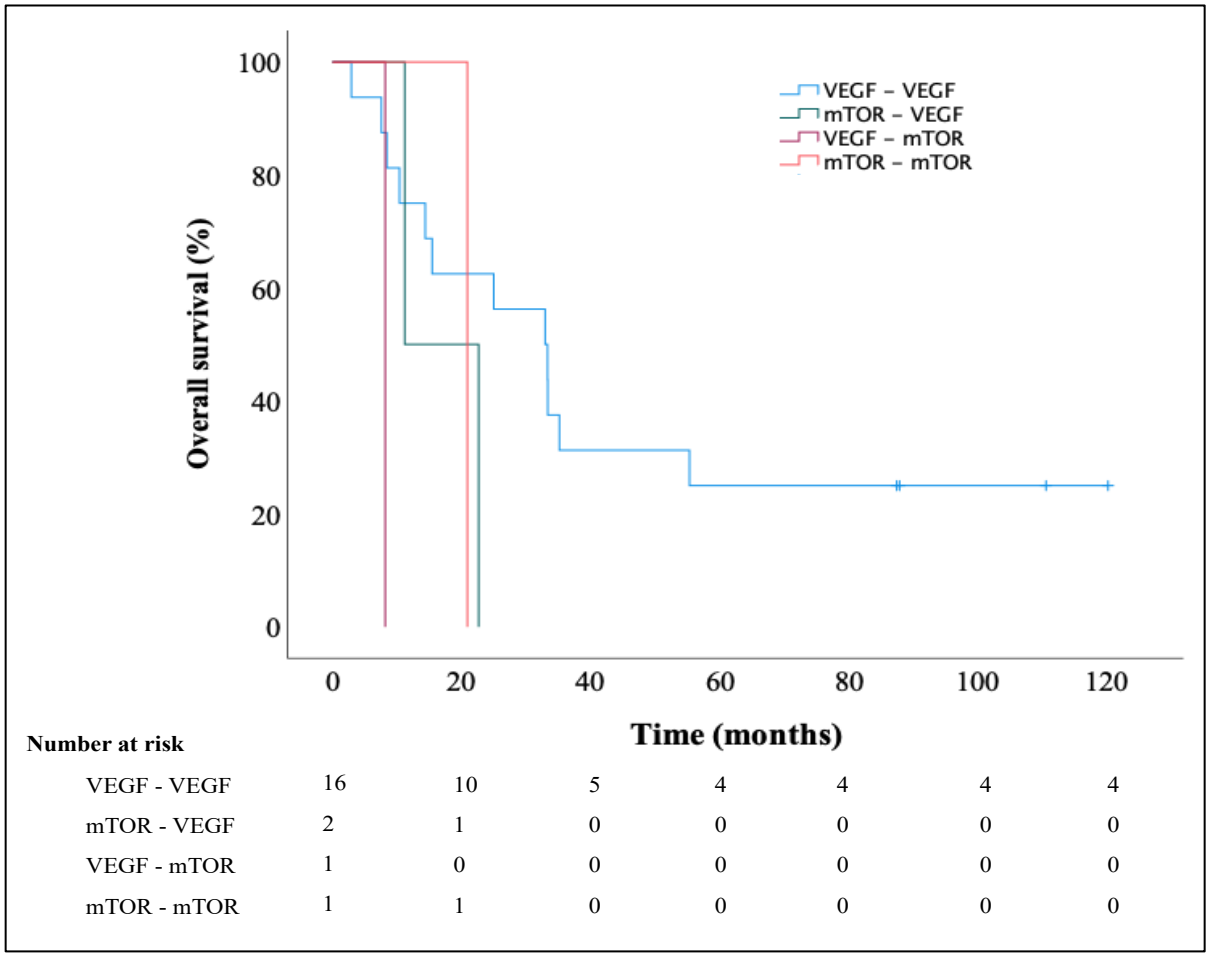


Figure 30 *- Sankey diagram outlining treatment patterns and outcomes according to first-line treatment agent.*

The most common therapy sequences were front-line VEGF- inhibitor followed by second line, VEGF-inhibitor (80%, 16/20). Two patients (10%) received front line mTOR followed b VEGF-inhibitor, one patient (5%) had VEGF-inhibitor followed by mTOR. Lastly, one patient (5%) had two different mTOR inhibitors used in the first- and second-line setting. The median OS was the longest (33.0 months (95%CI, 16.6-49.4) in the VEGF – VEGF group. There were no statistically significant differences amongst the sequencing groups (p=0.087), probably due to the overall low patient numbers in some of the subgroups **(Fig. 31).**



Number at risk							
VEGF - VEGF	16	10	5	4	4	4	4
mTOR - VEGF	2	1	0	0	0	0	0
VEGF - mTOR	1	0	0	0	0	0	0
mTOR - mTOR	1	1	0	0	0	0	0

Figure 31 *- Kaplan–Meier estimates of OS stratified by the therapy sequencing groups in the second line setting. Tick marks represent data censored at the last time the patient was known to be alive (at the time of data cut-off).*

Due to the low patient numbers, the analysis of therapy sequencing in the third line setting has very limited statistical value, however the overall trend showed that the majority of patients (44%, 4/9) received an mTOR inhibitor, after having progressed on two previous lines of VEGF-inhibitors. From the remaining patients 33% (3/9) received three subsequent lines of VEGF inhibition therapy. One patient (11%) had mTOR, followed by two lines of VEGF-inhibitor and one other patient (11%) had two lines of VEGF followed by third line ICI. There were no statistical differences between the therapy sequencing groups (p=0.296) **(Fig. 32)**.

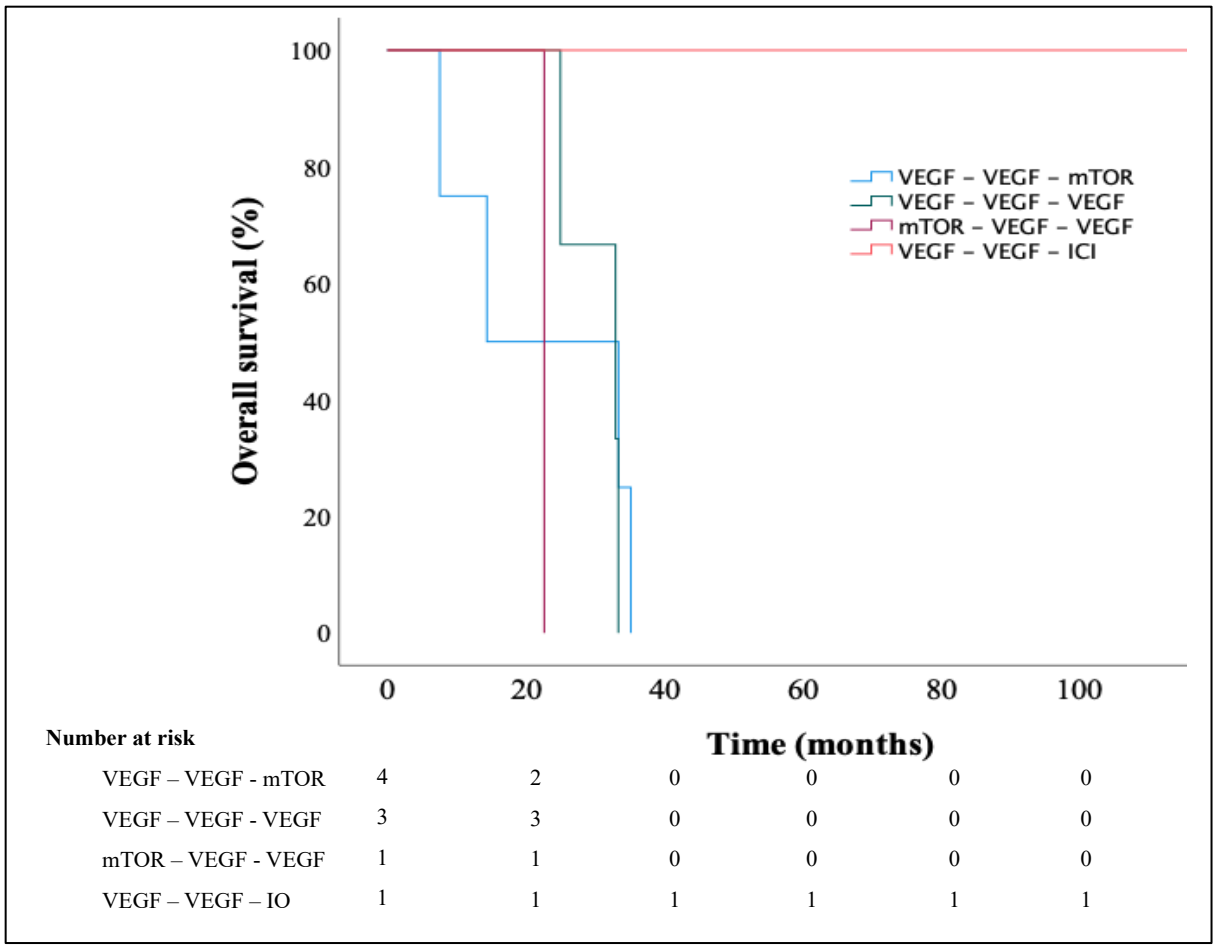


Figure 32 *- Kaplan–Meier estimates of OS stratified by the therapy sequencing groups in the third line setting. Tick marks represent data censored at the last time the patient was known to be alive (at the time of data cut-off).*

4.4.6. Baseline clinico-pathological variables and therapy choice predicting OS

Next the correlation between baseline clinico-pathological parameters, choice of front-line therapy and overall survival was explored. Multivariate survival analysis showed that patients with an ECOG performance status of 2, those with MSKCC poor risk and patients with lymph node metastasis had significantly shorter overall survival with a HR of 4.15 (95%CI, [1.22-14.13], p=0.023), 5.32 (95%CI, [1.60 – 17.69], p= 0.006) and 3.37 (95%CI, [1.05 – 10.90], p= 0.042), respectively. These variables were independent of known other determinants of overall survival such as patient age, higher Fuhrman nuclear grade, tumour size, upfront metastatic disease, or CNS metastasis (**Table 6**).

Table 6. Multivariate survival analysis (Cox regression model) of variables predicting outcome in terms of overall survival in patients with treatment naïve papRCC

Parameters	Hazard Ratio (HR)	95% confidence interval (CI)		p-value
		Lower	Upper	
Age <65 years	0.84	0.30	2.3	0.727
Gender Female	1.91	0.79	4.62	0.153
ECOG PS 2	4.15	1.22	14.13	**0.023**
MSKCC poor risk	5.32	1.60	17.69	**0.006**
IMDC poor risk	0.86	0.25	2.92	0.806
Previous nephrectomy	0.45	0.07	3.03	0.410
Fuhrman Grade 3	1.03	0.29	3.60	0.965
Tumour stage pT4	0.72	0.43	1.20	0.209
Upfront metastatic disease	1.20	0.45	3.15	0.724
Bone metastasis	2.72	0.73	10.14	0.137
Liver metastasis	0.73	0.20	2.63	0.630
Lung metastasis	1.62	0.62	4.20	0.322
Lymph node metastasis	3.37	1.05	10.90	**0.042**
CNS metastasis	1.02	0.18	5.90	0.981
TKI as first line therapy	0.38	0.10	1.45	0.157

CNS: central nervous system, ECOG: Eastern Cooperative Oncology Group, IMDC: International Metastatic RCC Database, MSKCC: Memorial Sloan-Kettering Cancer Centre, Consortium, PS: performance status, TKI: tyrosine kinase inhibitor.

5. DISCUSSION

Renal cell carcinoma is the 16th most frequent solid tumour neoplasm worldwide and accounts for 2.2% of all new cancer cases [1]. Approximately 30% of non- metastatic patients who underwent a nephrectomy in the curative setting will be diagnosed with metastasis [147]. The 10-year cancer specific survival of ccRCC and papRCC are 62% and 86%, respectively. The 10-year cancer specific survival of ccRCC and papRCC in the metastatic are 15% and 3% [148,149]. The predominant histological subtype is ccRCC representing approximately 80% of all cases. The remaining subtypes are grouped together and referred to as non-clear cell RCC. Among these, papRCC and chromophobe RCC are the most common subtypes representing approximately 15% and 5%, respectively [17].

From a histological perspective, papRCC is a diverse disease, encompassing tumours that present with a mild clinical course as well as those exhibiting an aggressive phenotype associated with high mortality. Data about the genetic basis of the above presentation has been lacking. Molecular characterization of almost 200 primary papRCC was performed using whole-exome sequencing, transcriptome sequencing and proteomic analysis. Type 1 papRCC were more likely to be lower- grade tumours associated with MET alterations and gain of chromosome 7. Type 2 tumours were characterized by CDKN2A silencing, SETD2 mutations, TFE3 fusions, and increased expression of the NRF2–antioxidant response element pathway. Type 2 papRCC was further classified into three individual subgroups where subgroup 1 was associated with an early stage of tumour development and DNA methylation. Subgroup 2 had more advanced tumours (stage III or IV), and mutation of SETD2. Subgroup 3 included CIMP-associated tumours. Patients with type 1 papRCC and tumours in subgroup 1 had the highest probability of OS. Patients in subgroup 2 had a lower survival rate and patients in the third subgroup showed the worst outcomes [25].

With the increased understanding of the underlying molecular pathways, the WHO classification has evolved and for the first time introduced a new group which describes the molecularly defined renal cell carcinoma subgroup. These tumours have a combination of unique morphological and immunohistochemistry findings but may also need genetic testing for further confirmation. Traditionally papRCC were classified into subtypes, 1 and 2. In the new 2022 WHO classification, type 1 is considered as the classic papRCC, and further subtyping is no longer recommended. This is largely due to the heterogeneity of tumours with mixed phenotypes and heterogenous molecular make-up within the type 2 papRCC subgroup. Numerous recently identified tumour types have been reclassified as distinct categories, no longer falling under the classification of type 2 papRCC. These are the fumarate hydratase (FH)-deficient RCC, tumours of the MiT family, the novel eosinophilic solid and cystic (ESC)-RCC, tubule-cystic RCC and collecting duct carcinomas. Overall, the spectrum of papRCC is expanding with emerging entities being described. Further studies are necessary to classify these as independent subtypes and define their prognostic value [17,150].

Surgical resection is the gold standard therapy for the treatment of localised RCC [135]. This strategy applies to all histological subtypes. There are no established perioperative therapies for papRCC. RAMPART (NCT03288532) is the only currently ongoing phase III, randomized trial which includes non-clear cell RCC. Patients with high risk of recurrence after surgical resection are randomized to receive single agent or doublet ICI therapy or undergo standard of care follow up with cross-sectional imaging only [151].

The treatment of metastatic papRCC is a complex issue. While targeted therapies such as VEGF-, mTOR inhibitors and ICIs are established treatment strategies in metastatic ccRCC, level 1 evidence is lacking in patients with non-clear cell RCC. Due to the much higher prevalence of clear cell histology, there is limited data on systemic therapy in patients with other renal cell carcinoma subtypes. Evidence is obtained from small single-arm trials, expanded access schemes and subgroup analysis of larger RCC studies. Therefore, most of the clinical decision making is extrapolated from clear cell subtype algorithms. At present, the most effective treatment approach for patients with papRCC is unknown.

Currently, systemic therapy options for non-ccRCC include cytokine-based immunotherapies, targeted therapies (including VEGF and mTOR inhibitors) and ICIs. Cytokine-based immunotherapy using high-dose IL-2 and IFN-α became the first systemic therapies approved for RCC. The trials showed some efficacy in ccRCC, but not in papRCC, therefore these are not recommended in this setting [152].

Three randomized trials investigated sunitinib and everolimus in papRCC [137–141]. ASPEN, ESPN, RECORD-3 all showed a higher PFS in sunitinib treated patients compared to everolimus with a HR of 1.41 (80% CI: 1.03–1.92), 1.16 (95% CI: 0.67–2.01) and 1.5 (95% CI: 0.9–2.8), respectively, [116,153,154]. Data on OS were reported by both ESPN and ASPEN, both favouring sunitinib with a median OS of 16.2 vs 14.9 months, and 31.5 vs 13.2 months, for ESPN and ASPEN trials, respectively.

The randomized multicentre phase 2 PAPMET trial investigated cabozantinib, crizotinib, sunitinib and savolitinib. At the interim analysis, savolitinib and crizotinib showed poor responses and these arms were closed for further recruitment. The trial was then re-designed into a 2-arm randomized trial comparing cabozantinib and sunitinib[155]. Cabozantinib outperformed sunitinib both for PFS (HR 0.60 [95%CI: 0.37–0.97], p = 0.019) and response rate (23% vs. 4%, p = 0.010). Savolitinib and crizotinib did not show any benefit when compared with sunitinib[142].

Savolitinib was then further investigated in a single-arm phase 2 trial in papRCC and showed that ORR increased from 7% to 18% in patients with MET-driven disease. The median PFS was also higher in MET-driven papRCC (6.2 vs 1.4 months, HR 0.33, [95% CI 0.2-0.52]) [156]. SAVOIR, a phase 3, randomized trial, compared savolitinib and sunitinib in patients with treatment naïve, metastatic MET-driven papRCC. Results showed favourable efficacy with savolitinib with an ORR of 27% compared to 7% for sunitinib (p= 0.048). The median PFS was 7.0 vs. 5.6 months, with a HR of 0.71 (95% CI: 0.37–1.36) in savolitinib and sunitinib, respectively. Similarly, median OS was higher in the savolitinib group with a HR of 0.51 (95% CI: 0.21–1.17) [143].

Immune checkpoint inhibitor-based combination therapies such as nivolumab/ipilimumab, nivolumab/cabozantinib, pembrolizumab/lenvatinib are approved for metastatic ccRCC and are reasonable therapy choice for papRCC even though outcomes are generally less favourable than in ccRCC. Front-line nivolumab/cabozantinib in papRCC patients showed high response rates (47.5%) and significantly increased survival with a median PFS of 12.5 months (95% CI, 6.3 to 16.4) and median OS of 28 months (95% CI, 16.3-NE) [145]. Lenvatinib/pembrolizumab showed similarly promising response rates (52.9%) though survival data is still immature [146]. Savolitinib combined with durvalumab showed high efficacy especially in MET-driven papRCC [143], and is currently tested in a three-arm, multicentre, phase III study (savolitinib/

durvalumab vs sunitinib and durvalumab monotherapy) in this patient population (SAMETA, NCT05043090) [157]

The aim of this dissertation was to analyse the outcome of patients with metastatic, type 2, papRCC who were treated between 2005 – 2015, in the Department of Urology, University Hospital Munich Grosshadern, Ludwig-Maximilians University. We aimed to compare the effectiveness of different systemic therapies used and describe outcomes such as response to therapy, PFS, and OS. We also analysed baseline clinical and pathological features which may influence patient outcomes. Moreover, my objective was to systematically review the relevant literature that compares the oncological outcomes of various systemic therapies metastatic papRCC, with the intention of contextualizing this research appropriately.

This is a retrospective, single centre audit with data collected over a period of 10 years. The median follow-up for this patient population was 71 months (95%CI, 24-118) which is the longest reported in the current literature. Baseline patient and tumour characteristics are similar to those previously described in the literature [137].

The median DFS was 14.9 months (95% CI, 2.5 – 27.3) and 43% of patients developed metastatic disease after initial surgery with curative intent. This underpins the importance of perioperative therapy for these patients with high risk of relapse. Neoadjuvant therapy is controversial in RCC. Neoadjuvant axitinib was investigated in the NAXIVA trial (NCT03494816), axitinib/avelumab in the NeoAvAx trial (NCT03341845), finally a combination of neoadjuvant and adjuvant nivolumab in the PROSPER trial (NCT03055013) [158–160]. All these studies were conducted in patients with ccRCC only. There are no neoadjuvant studies in patients with papRCC or other non-ccRCC subtypes. Similarly, there is also no data for the use of adjuvant therapy in papRCC. RAMPART (NCT03288532), a phase III multi-arm trial of adjuvant ICIs is currently the only study which allows recruitment of all subtypes of RCC [151].

Until recently, CN in patients with upfront metastatic RCC was part of standard therapy [90]. In our patient cohort, median OS for patients with CN was 9.8 compared to 7.7 months in the no- CN group ($p=0.777$). Data collected by the IMDC collaborative group showed a significant difference (16.3 vs 8.6 months, $p < 0.0001$) in patients with metastatic papRCC [161]. Differences between our findings are most likely due to the significantly higher patient number included in the IMDC database.

All patients received front-line therapy, however the number of patients receiving subsequent therapies after progression is smaller than in patients with metastatic ccRCC [133]. Only 48% received second line, 21% received third line and 5% received fourth line, subsequent therapies. This is most likely due to the aggressive nature of papRCC and lack of effective therapy options.

The median overall survival in our patient cohort was 10.5 months (95%CI, 5.4 – 15.7). The percentage of patients who were alive at 1 year, 2 years and 5 years were 41%, 31% and 5%, respectively.

Sunitinib was the most frequently used first line therapy agent in 74% of patients. Amongst the patients who received front line VEGF inhibitors (sunitinib, sorafenib, pazopanib), only the sunitinib treated patients demonstrated response to therapy. The ORR in these patients was 26% with 10% achieving complete response. Consequently, in our patient population sunitinib seems to be the most effective first line therapy. This is in line with data from the ASPEN trial where patients with pure papRCC had a response rate of 24%. The median PFS of patients in

the sunitinib group was 7.1 months (95%CI, 4.0-10.2) which is again comparable to the results seen in ASPEN (10.4 months (95%CI, 9.6-11.3)). The median OS in the trial was significantly longer, 31.5 months (95%CI, 14.8–NR), compared to 10.4 months (95%CI, 9.6-11.3) in our series.

After disease progression, the most commonly used second line therapy were again VEGF-inhibitors (sorafenib and axitinib). Only two patients received a treatment with a change in the mechanism of action and went on to subsequent mTOR inhibitor therapy. The ORR in the second line setting was 0%, however 70% of patients still achieved stable disease. The median PFS and OS in this setting were 8.4 months (95%CI 3.3 – 13.4) and 8.8 months (95%CI), 4.2 – 13.4)., respectively. These are relatively long survival which probably explained by the highly selected nature of patients who are fit enough to receive subsequent therapy. Similarly, in the third line setting, everolimus was used most frequently (44%). No responses were seen in either of the therapy groups, however 78% of patients achieved stable disease. The median PFS and OS in the third line were 5.4 months (95%CI 0.5 – 10.5) and 5.3 months (95%CI, 4.2 – 6.5), respectively. Data on the efficacy of subsequent therapies following progression on front-line theray in metastatic papRCC are lacking. Retrospective cohort studies showed that subsequent use of cabozantinib is associated with clinical benefit with notable response rates (14.3-26.8%) and PFS (7-8.6 months) [162,163]. The most common sequencing regimen in our cohort was VEGF → VEGF in the second line and VEGF → VEGF → mTOR in the third line setting.

Overall, there are numerous uncertainties in the treatment of metastatic papRCC. Notably the question of the most effective first line agent and the choice of subsequent therapies remain unsolved. It is likely that as the combination of ICI and VEGF inhibitor has changed the therapy landscape of ccRCC, it will also be increasingly used in papRCC or other histological subtypes. Data shows that currently the most effective treatment regimens are nivolumab/cabozantinib and lenvatinib/pembrolizumab with similar ORR of 47.5% and 52.9%, respectively. The median PFS with nivolumab/cabozantinib was 12.5 months (95% CI, 6.3 to 16.4) and median OS was 28 months (95% CI, 16.3-NE) [145]. The 6-month PFS with lenvatinib/pembrolizumab was 72.3% (95% CI, 60.7-81.0) and the 6-month OS rate was 87.8% (95% CI, 78.5-93.2) [146]. On the whole data on ICI and VEGF inhibitor combination therapies are still immature and none of these agents are approved by the regulatory agencies.

Despite several strengths, this analysis is not devoid of limitations. This includes the retrospective nature of the data collection, and the relatively modest patient cohort size. Furthermore, there were no cabozantinib treated patients as this therapy option was not approved at the time. The relatively long survival in some of the patients is attributed to the heavy selection bias.

Over the past years, thanks to the advancements in the fields of molecular biology, massive amount sequencing data has been generated at a fraction of the price. It is likely that sequencing will be increasingly used to identify molecular alterations in renal tumours which will lead to the development of more targeted therapies. The use of savolitinib in MET-driven tumours in the SAVOIR and SAMETA trials are just the earliest steps taken in this direction.

6. CONCLUSION

The treatment landscape of papRCC has changed significantly over the past decade, but randomized phase III trials in papRCC-only patients are still lacking. Until recently, the clinical evidence for the treatment of metastatic papRCC was derived from small, randomized trials such as ESPN, ASPEN, RECORD-3 which compared sunitinib vs everolimus. These trials broadly demonstrated a superior outcome in patients receiving sunitinib compared to everolimus.

Over the past 5 years, the number of clinical trials conducted in patients with metastatic papRCC has significantly increased. PAPMET, a trial which only included patients with histologically confirmed papRCC established cabozantinib as a standard of care for front-line therapy. SAVOIR, a trial which for the first time used a genomic-directed therapy, instead of a histology-driven approach, showed a significant response with savolitinib in patients with MET-driven disease biology. Responses were even higher when patients received combination savolitinib/durvalumab.

Immunotherapy alone has a significant activity in papRCC as demonstrated by the Keynote-427 trial. However, combination of immunotherapies with a CTLA-4 antibody seem to have less favourable responses with significantly higher toxicity. When combining immunotherapy with VEGF inhibitors, multiple phase 2 trials have demonstrated significant activity in papRCC with the highest response rates shown when receiving lenvatinib/pembrolizumab. There are currently a plethora of ongoing clinical trials using doublet ICI/VEGF (PAPMET 2, NCT02761057), doublet ICI (SUNIFORCAST, NCT03075423) and doublet ICI/MET-inhibitor (SAMETA, NCT05043090) combinations and their results are eagerly anticipated.

Papillary renal cell carcinoma is a heterogenous group which encompasses multiple histological subtypes. Owing to recent molecular studies, this in now recognized and reflected in the most recent, 2022 WHO renal cell carcinoma classification. Further characterization of these tumours is critical to develop genomic subtype directed personalized therapy.

This retrospective analysis conducted at a single centre, coupled with a comprehensive literature review, provides a robust summary of the existing evidence base for systemic therapies in metastatic papRCC. Our results showed that VEGF-inhibitors are effective and have superior outcomes with regards to response rate and survival when compared to mTOR inhibitors. ICI and VEGF inhibitor combination therapies will likely replace the current therapy regimens in the future. Sequencing and molecularly targeted therapies will be part of the personalized cancer care in patients with metastatic papRCC. Due to their relatively low prevalence, the treatment of papRCC and other non-ccRCC subtypes are understudied and constitute a significant unmet need. Further research via large international, collaborative groups delivering randomized controlled trials are essential in order to advance this field.

7. LIST OF ABBREVIATIONS

BMI	Body-mass index
ccRCC	Clear cell renal cell carcinoma
chRCC	Chromophobe renal cell carcinoma
CI	Confidence interval
CN	Cytoreductive nephrectomy
CR	Complete response
CSS	Cancer- specific survival
CT	Computed tomography
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
DFS	Disease free survival
ESRD	End-stage renal disease
HIF	Hypoxia-inducible factor
HLRCC	Hereditary leiomyomatosis and renal cell carcinoma syndrome
HR	Hazard ratio
ICI	Immune checkpoint inhibitors
IFN-α	Interferon alfa
IL-2	Interleukin-2
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
ISUP	The International Society of Urological Pathology
MET	Methyl- nitroso- nitroguanidine
MSKCC	Memorial Sloan Kettering Cancer Centre
mTOR	Mammalian target of rapamycin
non-ccRCC	Non-clear cell renal cell carcinoma
ORR	Overall response rate
OS	Overall survival
papRCC	Papillary renal cell carcinoma
PD	Progression of disease
PD-1	Programmed Death-1
PD-L1	Programmed Death ligand - 1
PFS	Progression- free survival
PR	Partial response
RCC	Renal cell carcinoma
SD	Stable disease
TNM	Tumour Node Metastasis
UICC	Union for International Cancer Control
VEGF	Vascular endothelial growth factor
VHL	von Hippel- Lindau
WHO	World Health Organization

8. LIST OF FIGURES AND TABLES

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Affidavit

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I hereby declare, that the submitted thesis entitled

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