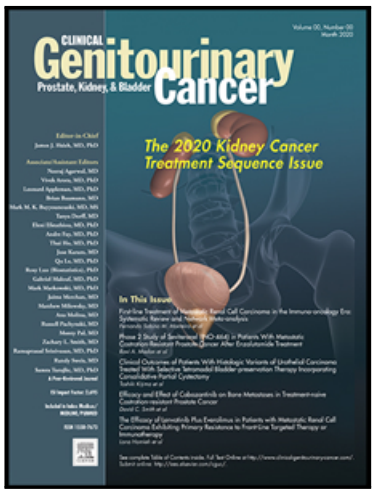

Patient characteristics, treatment patterns, and outcomes for patients with renal cell carcinoma in England: a retrospective cohort study

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PII: S1558-7673(24)00052-1
DOI: https://doi.org/10.1016/j.clgc.2024.102081
Reference: CLGC 102081

To appear in: *Clinical Genitourinary Cancer*

Received date: Jan 25, 2024
Revised date: Mar 11, 2024
Accepted date: Mar 15, 2024

Please cite this article as: Prantik Das , Alison Booth , Robert Donaldson , Noami Berfeld , Beth Nordstrom , Robert Carroll , Poonam Dhokia , Andrew Clark , Luis Vaz , Patient characteristics, treatment patterns, and outcomes for patients with renal cell carcinoma in England: a retrospective cohort study, *Clinical Genitourinary Cancer* (2024), doi: https://doi.org/10.1016/j.clgc.2024.102081

Title: Patient characteristics, treatment patterns, and outcomes for patients with renal cell carcinoma in England: a retrospective cohort study

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Abstract word count: 248

Text word count: 2529

Take Home Message:

- Survival for patients with de novo metastatic disease remains poor, highlighting the need for earlier diagnosis and intervention.
- Patients diagnosed at earlier stages have considerably longer survival, especially among those who received nephrectomy.
- Poorer survival was associated with lower socioeconomic status, highlighting an unmet need.

CONFLICT OF INTEREST PAGE

Author contributions

All authors provided substantial contributions to the conception and design of the work, and interpretation of results and were involved in the review and approval of this manuscript for publication. Alison Booth and Robert Donaldson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial disclosures

Alison Booth, Beth Nordstrom, Noami Berfeld and Robert Donaldson are employees of Evidera. Evidera received funding from BMS for the project reported in this manuscript.

Funding/Support and Role of Sponsor

Funding for this study was provided by BMS. The sponsor contributed to the study design and interpretation of results.

ABSTRACT

Background and Objective: Considering the rapidly evolving treatment landscape of renal cell carcinoma (RCC), recent descriptions of the RCC population in the UK are lacking, as are real-world data on treatment and patient outcomes. To analyse the demographic and clinical characteristics, treatment patterns, and overall survival of patients with RCC using national data sets in England.

Patients and Methods: This was a retrospective cohort study of patients diagnosed with RCC (all stages) between 2014-2018 using demographic, clinical, cancer registration, and treatment data. Patients were followed until death or study end (31 December 2020). Treatments administered in each line were described to understand treatment sequencing. Kaplan–Meier methods were used for time-to-event analyses. Factors associated with discontinuation and survival were identified using Cox proportional hazard models.

Results and Limitations: Among 32,577 included patients, the median age at diagnosis was 66 years, 63.4% were male, and 6,786 (20.8%) had metastatic RCC at diagnosis. Tyrosine kinase inhibitor (TKI) monotherapy was the most common treatment class across lines. Over three quarters of patients (78.5% [95% CI 78.0–78.9]) were alive one year after diagnosis (93.2% in the non-metastatic at diagnosis subgroup and 37.1% among patients with metastases at diagnosis). At three years post initial diagnosis, 18.0% patients were alive in the metastatic at diagnosis subgroup. Rapid evolution of the treatment landscape limits the results regarding lines of therapy.

Conclusion: This large-scale study provides insight on characteristics of patients with RCC, and it highlights the need for better treatment options to improve survival.

Keywords

England, Real-world data; Kidney Cancer, Targeted therapy, Immunotherapy

MICROABSTRACT

Treatment pathways and survival outcomes were assessed for patients with the most common form of kidney cancer (renal cell carcinoma) in England using national data. In total, 32,577 patients were included. Over three quarters of patients were alive one year after diagnosis (93.2% in the non-metastatic subgroup and 37.1% among patients with metastases at diagnosis).

CLINICAL PRACTICE POINTS

This study used large-scale national data regarding recent treatment and survival of over 30,000 patients with RCC Information generated from this study provides insight on characteristics of patients with RCC, and highlights populations with potentially unmet needs regarding treatment persistence and survival.

This study provides insight on the changing patterns of RCC management and evaluated the role of nephrectomy in advanced and metastatic disease. The study shows use of novel therapies emerging in both first and subsequent lines of therapy. A shift from TKI monotherapy is expected to continue with expanding approval and reimbursement for combination therapies. Survival among patients with de novo metastatic disease remains poor, highlighting the need for earlier diagnosis and intervention. Patients diagnosed at earlier stages had considerably longer survival, especially among those who received a nephrectomy. The unmet need is also seen in the consistent finding of poorer survival for patients with lower socioeconomic status.

Owing to this rapidly evolving treatment landscape, further research is required to understand changes in treatment patterns and outcomes with the more recently approved therapies that could

not be fully captured in this study and the reasons for the disparity in patient outcomes across socio-economic groups.

INTRODUCTION

Kidney cancer is the seventh most common cancer in England, with 29,139 new cases between 2018 and 2020 [1]. Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for 80% of cases [2]. It is estimated that approximately 30% of patients have metastatic disease at the time of diagnosis [3-5]. The overall 5-year survival rate of patients with RCC in England is 65%, ranging from 10% in patients with metastatic disease at diagnosis to 85% in patients with stage 1 disease at diagnosis in 2019 [6]. Given the evolving treatment landscape for RCC, understanding the real-world use of novel therapies is important. At the time of this study, nephrectomy was the preferred disease management for localised/locally advanced RCC, whereas for advanced/metastatic disease, systemic treatment with immuno-oncology (IO) and/or targeted therapies was recommended [7]. Treatments for advanced/metastatic patients are often driven by prognostic risk assessments [8,9]. In favourable-risk patients with clear cell RCC, vascular endothelial growth factor inhibitors were the recommended first-line treatment; [8] in intermediate/poor-risk patients, the combination of nivolumab plus ipilimumab (NICE approval April 2019) were the recommended first-line treatment. Cabozantinib was approved by NICE (October 2018) for first-line treatment for intermediate- and poor-risk patients. For subsequent lines of therapy, nivolumab monotherapy (NICE approval October 2016) [10], or the tyrosine kinase inhibitors (TKIs) cabozantinib (NICE approval August 2017) [11] and axitinib (NICE approval February 2015) were some of the therapy options [12]. The reimbursement (September 2020) of the IO+TKI combination avelumab + axitinib, as part of the Cancer Drugs

Fund (CDF) has more recently impacted the treatment landscape. At the time of conducting this study, there were no approvals by the EMA or NICE for adjuvant/systemic treatment of local disease.

This study used national data to describe the demographic and clinical characteristics, treatment patterns, and overall survival (OS) of patients with RCC in England.

MATERIALS AND METHODS

This was a retrospective observational cohort study of patients diagnosed with RCC between 2014 and 2018.

Data sources

Pseudonymised linked data were used from the National Cancer Registry and Analysis Service (NCRAS), Systemic Anticancer Therapy (SACT) dataset, and Hospital Episode Statistics (HES) outpatient and admitted patient care. Registry data include patient demographic information, and cancer-specific details including tumour site, diagnosis date, stage at diagnosis, and histology. SACT data include information on use of treatments such as such as chemotherapy, targeted therapy, and immunotherapy. In the National Health Service (NHS), the publicly funded healthcare system in the UK, information on prescribed anti-cancer therapy must be submitted to the SACT dataset. HES data include information on outpatient visits, inpatient admissions, procedures, and diagnoses.

Study population

Eligible patients were Ó 18 years old, with histologically confirmed RCC diagnosed between 1 April 2014 and 31 December 2018, based on International Classification of Diseases for Oncology, Third Edition codes (supplementary materials Table A1). Patients were excluded if

diagnosed with a primary tumour other than RCC on or before RCC diagnosis, or if the RCC diagnosis occurred at autopsy. The date of initial RCC diagnosis was the index date, and patients were followed until the earliest of death or 31 December 2020. Patients were assigned to mutually exclusive metastatic (stage 4), or non-metastatic (stages 1-3) subgroups based on metastatic status and disease stage at diagnosis in the NCRAS data. Patients lacking the respective information were not included in either subgroup.

Key variables

Baseline demographic and clinical characteristics were obtained from NCRAS data. Socioeconomic status was derived using the Index of Multiple Deprivation, as provided by the cancer registry. This index classifies the deprivation of geographical areas, , with ñquintile 1ò representing the least deprived areas and ñquintile 5ò representing the most deprived areas. Patient nephrectomy status was identified by the presence of at least one record of nephrectomy in HES Admitted Patient Care data at any time from one month before the qualifying RCC diagnosis. Treatment patterns were assessed for up to three lines of therapy, and treatment regimens were categorised per Table 1. Any treatment regimen including targeted therapy was considered a targeted regimen; regimen containing an IO but no targeted therapy were classed as IO regimen. A new treatment line was defined as starting a regimen containing one or more drugs new to the patient or having a gap of more than 120 days and restarting the same regimen. Dropping a treatment from a combination did not signal a new line of therapy. Death, starting a new regimen, or no administration of a regimen in 120 days was used as indication of discontinuation. Time-to-treatment discontinuation was the time from the date of the treatment line initiation to the earliest of end of treatment line, or the date of death. OS was assessed from

the index date and from the start of each treatment line. Individuals who were alive at the end of follow-up were censored on the last day of available data.

Data analysis

All analyses were conducted in SAS® version 9.4 (SAS Institute, Cary, NC, USA). Demographic and clinical characteristics, time to discontinuation, and OS from diagnosis of patients with RCC were compared between subgroups using non-parametric and semi-parametric methods. KaplanïMeier methods were used for time-to-event analyses. Factors associated with discontinuation and OS were assessed using univariable and multivariable Cox proportional hazards models. A significance level of 0.05 was used as the criterion for determining variable entry and removal from the multivariable models, however, age and sex were included a priori.

Ethical conduct

This study received approval from the Research Ethics Committee in the UK, and pseudonymised data were transferred from NCRAS via a secure transfer. Given the study design, informed consent was not required. Small patient numbers (Ò 5) were suppressed to protect anonymity.

RESULTS

Patient characteristics

Overall, 32,577 patients were included in the study, of whom 21,825 (67.0%) had non-metastatic RCC at diagnosis, and 6,786 (20.8%) had metastatic RCC at diagnosis. Median age at diagnosis was 66 years (standard deviation = 13.4), and most patients were male (n = 20,642; 63.4%). Most patients had a clear-cell histology (81.4%). Patients with metastatic disease at diagnosis were older than patients with non-metastatic disease at diagnosis ($p < 0.001$). Most patients were

white, which was consistent across subgroups. Nephrectomy was most common among patients who had non-metastatic disease at diagnosis. Table 2 outlines patient characteristics.

Treatment patterns

The most commonly observed treatment pathway was TKI monotherapy at first-line (pazopanib or sunitinib) to IO monotherapy (nivolumab) at second-line (Figure 1).

First-line systemic treatment

Among all patients, 5,657 patients had a first-line systemic treatment recorded in SACT data (n = 4,997 [88.3%] clear cell; n = 439 [7.8%] non-clear cell). Among patients who received systemic therapy during follow-up, over three quarters received TKI monotherapy as their first-line systemic treatment (n = 4,313; 76.2%) (Figure 1). Pazopanib was the most common TKI treatment received (37.6%) followed by sunitinib (31.8%) (Table 3**).** Over half of patients (59.9%; 95% confidence interval [CI]: 58.6ï61.2) persisted on first-line treatment for three months from initiation. This decreased to 38.3% (95% CI: 37.0ï39.6) and 18.0% (95% CI: 17.0ï 19.1) at six and 12 months, respectively. In multivariable analyses, older age, later year of diagnosis, non-clear cell histology, and tumour grade 3, 4, or unknown at diagnosis were associated with increased risk of first-line treatment discontinuation (Figure 2).

Second-line systemic treatment

Less than half of patients who received first-line systemic therapy received a second-line (n = 2,606; 46.1%). Of those with a second-line therapy, 89.5% (n = 2,333) had clear cell histology and 7.1% (n = 186) had non-clear cell histology. Nivolumab was the most frequently used specific treatment (25.1%) (Figure 1). While TKI monotherapy was still the most common class of treatment, an increase in the proportion of patients receiving IO monotherapy was observed

(Table 3). The most frequently received second-line TKI therapies were axitinib (19.9%) and cabozantinib (15.9%). At 12 months from initiation, 19.0% (95% CI: 17.5ï20.7) of patients persisted on second-line therapy. In multivariable analyses, non-clear cell histology and no nephrectomy before treatment initiation were associated with increased risk of second-line treatment discontinuation.

Third-line systemic treatment

Of patients who received second-line treatment, over one third (n = 989; 38.0%) received third-line therapy (n = 894 [90.4%] clear cell; n = 69 [7.0%] non-clear cell). At third-line, nivolumab was the most common (36.1%) specific treatment while TKI monotherapy and IO monotherapy were the most common treatment classes (Table 3, Figure 1). At 12 months from initiation, 20.5% (95% CI: 17.8ï23.4) of patients persisted on third-line therapy. In multivariable analyses, later year of diagnosis, non-clear cell histology, and no nephrectomy before treatment initiation were associated with increased risk of third-line treatment discontinuation.

OS

From the initial RCC diagnosis, 78.5% of patients (n = 25,566; [95% CI 78.0ï78.9]) were alive after one year. At three years post-diagnosis, 84.5% of patients in the non-metastatic at diagnosis subgroup were alive, while 18.0% of patients in the metastatic at diagnosis subgroup were alive (Figure 3). In multivariable analyses, age Ó 75 years and no nephrectomy were associated with increased risk of death. In patients diagnosed with metastatic or with non-metastatic disease, not having a nephrectomy was associated with a nearly two-fold increase in the risk of death (hazard ratio [HR] 1.99 [95% CI: 1.81ï2.18] and HR 1.93 [95% CI: 1.78ï2.08], respectively).

Among patients who were non-metastatic at diagnosis, the risk of death increased with a higher tumour grade, stage at diagnosis and increased deprivation. Increasing deprivation quintile was associated with increased risk of death among patients who were metastatic at diagnosis (Supplementary material Figure A2).

DISCUSSION

This retrospective study using national data from England presents treatment patterns and survival data of over 30,000 patients with RCC. Of the study cohort, 78.5% were alive one year after the date of diagnosis. For adults diagnosed with kidney cancer between 2015 and 2019, the NHS age-standardised estimate of one-year net survival was approximately 80% [13], similar to our findings. [13] Lower socioeconomic status was associated with a higher risk of mortality, compared to higher socioeconomic status. In addition, among the metastatic subgroup, associations were observed between the risk of survival and some geographic areas. Few studies examine factors associated with mortality in patients with RCC, particularly using recent data, which precludes further comparisons with the results of our study.

In the present study, 56% and 16% of patients with non-metastatic and metastatic disease, respectively, underwent nephrectomy. Over 80% of patients did not receive a systemic therapy during follow-up. Among patients who did receive systemic therapies, 88.3% (n = 4,997) had clear cell RCC. Sunitinib and pazopanib were the most common first-line treatments, likely due to the timing of treatment availability. Nivolumab plus ipilimumab usage was limited, likely reflective of the short time between the NICE conditional approval in 2019 and the restricted population for conditional reimbursement by the end of our study period [14]. Likewise, while some use of axitinib plus avelumab was observed, the study period ended a few months after NICE conditional approval in 2020 [15]. The choice of TKI therapy appeared to shift to

cabozantinib or axitinib in the second and third lines of therapy. At the second and third lines of therapy, increased use of nivolumab was observed, in line with treatment recommendations.

Real-world treatment persistence data in patients with RCC are lacking. A retrospective study from Spain among 46 patients with advanced RCC between 2019 and 2020 reported median persistence on TKI of 13 months (95%CI 5.4 - 20.6) [16]. In our study, at 3 months after initiation only 56% of metastatic patients remained on first-line treatment, and 58% for second-line treatment. Differences in study populations, sample size and study period may account for differences observed between studies. Persistence in our study appeared to increase with increasing line of therapy; the opposite of the trend expected based on clinical practice. A possible explanation is that as more treatment options are being approved for use in early lines of therapy, clinicians are more likely to switch patients to alternative treatments sooner when treatment response is suboptimal, compared to later lines when fewer options are available. This is supported by our finding that discontinuation appeared to increase with later years of diagnosis. Persistence by specific treatment regimen was not explored in this study. Additionally, the study shows the use of novel therapies emerging in both first and subsequent lines of therapy; consistent with Ratta et al., which reported an increase in the number of treatment lines over the years [17].

In cancer registration statistics for England, stage at diagnosis was lacking for over 30% of patients diagnosed in 2019; this was less than 15% in the present study [18]. Discrepancies regarding missingness between our study and the 2019 cancer registration statistics may be due to variation in reporting over time. Most patients in the current study were diagnosed with non-metastatic disease, and of those, 90% had no recorded systemic therapy.

Disease stage, an important prognostic factor, was only available at initial diagnosis. Therefore, it was not possible to identify progression, and it is likely that patients with non-metastatic disease at diagnosis who received systemic therapy during follow-up progressed to metastatic disease. The data contained limited information on the medical history of patients and lacked clinical data such as risk scores used for treatment decision-making and reimbursement, as well as laboratory and biomarker data. Contribution of SACT data was not mandated until April 2014, with most trusts conforming by July 2014. Therefore, treatment data from the first year of the study was less complete than data from subsequent years. There are also gaps in orally administered treatments in SACT due to trust-level operational reasons. Some restrictions are in place in SACT data regarding treatments received that are part of the CDF. As a result, it is expected that this study underestimates real-world use of IO-IO and IO-TKI combinations in addition to cabozantinib for the earlier years of the study. In addition, embarkation of patients was unattainable. Lag in data availability should be noted. Lastly, lines of therapy were derived using an algorithm that may not accurately reflect the clinical definition of a new line of therapy versus reintroduction of prior therapies. The present study has several key strengths. The cancer registration data cover the entire population of England; not only does this constitute the largest possible sample size for this study, but the results are likely to be generalisable. Furthermore, many variables included in this study are not available in large secondary care databases in the UK, allowing for a more granular description of the patient population and outcomes. While such information may be obtainable using site-based methods, the sample size would be considerably smaller than that available through NCRAS and SACT data.

This study provides comprehensive insight into the treatment landscape, patient demographics, socioeconomic status, and survival in the period prior to the adoption of immunotherapies as a

first line treatment and the approval of new TKIs. While we acknowledge that the treatment landscape has continued to evolve since data collection ended, our research serves as a fundamental starting point for future investigations, and we recommend that future research focus on the changes in treatment patterns and outcomes associated with the more recently approved therapies.

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TABLES

Table 1. Treatment categorisations

Category	Sub-category	Example regimens
Targeted monotherapy	TKI	Axitinib*, cabozantinib, pazopanib**, sunitinib, tivozanib**
	Anti-VEGF	Bevacizumab
	mTORi	Everolimus*
	Other	--
Targeted combination	--	Axitinib + avelumab**
IO monotherapy	--	Nivolumab*
IO combination	--	Nivolumab + ipilimumab**
Other^		
Unknown		

IO = immuno-oncology; mTORi = mechanistic target of rapamycin inhibitor; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor

* Reimbursed only for previously treated patients

** Reimbursed for first-line only

^ Any non-targeted or non-immuno-oncology treatment regimen in the Systemic Anti-Cancer Therapy data.

Table 2. Baseline demographic and clinical characteristics of patients with RCC, by metastatic status at diagnosis

Characteristics	**Overall cohort (n = 32,577)**	**By non-metastatic/metastatic subgroup at diagnosis**		
		Non-metastatic (n = 21,825)	**Metastatic (n = 6,786)**	***p*-value**
Sex				
Male	20,642 (63.4)	13,661 (62.6)	4,492 (66.2)	< 0.001*
Female	11,935 (36.6)	8,164 (37.4)	2,294 (33.8)	
Age (years) at diagnosis, median (IQR)	67 (56-76)	65 (55-74)	69 (59-77)	< 0.001^
Ethnicity, n (%)				
White	28,047 (86.1)	18,944 (86.8)	6,023 (88.8)	< 0.001*
Non-white	2,367 (7.3)	1,698 (7.8)	382 (5.6)	
Unknown	2,163 (6.6)	1,183 (5.4)	381 (5.6)	
Year of diagnosis, n (%)				
2014	5,205 (16.0)	3,242 (14.9)	1,098 (16.2)	< 0.001^
2015	6,728 (20.7)	4,440 (20.3)	1,517 (22.4)	
2016	6,831 (21.0)	4,677 (21.4)	1,449 (21.4)	
2017	6,897 (21.1)	4,723 (21.6)	1,411 (20.8)	
2018	6,916 (21.2)	4,743 (21.7)	1,311 (19.3)	
SES Quintile, n (%)				
Q1 (least deprived)	6,178 (19.0)	4,122 (18.9)	1,243 (18.3)	< 0.001^
Q2	6,838 (21.0)	4,631 (21.2)	1,410 (20.8)	
Q3	6,624 (20.3)	4,420 (20.3)	1,422 (21.0)	
Q4	6,526 (20.0)	4,406 (20.2)	1,353 (19.9)	
Q5 (most deprived)	6,276 (19.3)	4,217 (19.3)	1,355 (20.0)	
Missing	135 (0.4)	29 (0.1)	<5	

Characteristics	**Overall cohort (n = 32,577)**	**By non-metastatic/metastatic subgroup at diagnosis**		
		Non-metastatic (n = 21,825)	**Metastatic (n = 6,786)**	***p*-value**
Geographic region, n (%)				
North East	1,920 (5.9)	1,410 (6.5)	419 (6.2)	
North West	4,599 (14.1)	3,134 (14.4)	917 (13.5)	
Yorkshire and the Humber	3,564 (10.9)	2,481 (11.4)	760 (11.2)	
East Midlands	2,765 (8.5)	1,602 (7.3)	613 (9.0)	
West Midlands	3,319 (10.2)	2,229 (10.2)	785 (11.6)	< 0.001*
East of England	3,560 (10.9)	2,467 (11.3)	808 (11.9)	
London	3,744 (11.5)	2,538 (11.6)	611 (9.0)	
South East	5,434 (16.7)	3,477 (15.9)	1,073 (15.8)	
South West	3,672 (11.3)	2,487 (11.4)	800 (11.8)	
Stage at diagnosis, n (%)				
Stage 1	13,156 (40.4)	13,155 (60.3)	Ò5	
Stage 2	2,552 (7.8)	2,552 (11.7)	0 (0.0)	
Stage 3	5,707 (17.5)	5,701 (26.1)	Ò5	< 0.001^
Stage 4	7,014 (21.5)	251 (1.2)	6,763 (99.7)	
Unknown	4,148 (12.7)	166 (0.8)	16 (0.2)	
Tumour grade, n (%)				
G1 = Well differentiated	1,428 (4.4)	1,115 (5.1)	106 (1.6)	
G2 = Moderately differentiated	7,310 (22.4)	6,112 (28.0)	552 (8.1)	
G3 = Poorly differentiated	8,075 (24.8)	6,305 (28.9)	1,282 (18.9)	< 0.001*
G4 = Undifferentiated or anaplastic	2,579 (7.9)	1,687 (7.7)	781 (11.5)	
Not classified as above	237 (0.7)	123 (0.6)	82 (1.2)	
Not assessed	12,948 (39.7)	6,483 (29.7)	3,983 (58.7)	

Characteristics	**Overall cohort (n = 32,577)**	**By non-metastatic/metastatic subgroup at diagnosis**		
		Non-metastatic (n = 21,825)	**Metastatic (n = 6,786)**	***p*-value**
Histology, n (%)				
Clear cell	26,516 (81.4)	18,377 (84.2)	5,495 (81.0)	< 0.001*
Non-clear cell	2,499 (7.7)	1,756 (8.0)	410 (6.0)	
NA	3,562 (10.9)	1,692 (7.8)	881 (13.0)	
Nephrectomy, n (%)				
Yes	14,328 (44.0)	12,235 (56.1)	1,073 (15.8)	< 0.001*
No	18,249 (56.0)	9,590 (43.9)	5,713 (84.2)	

anon. = anonymous; IQR = interquartile range; SES = socioeconomic status

* Chi-squared test

^ Mann-Whitney *U* test

Table 3. Treatment regimen for first, second, and third line of therapy among patients who received systemic therapy during follow-up

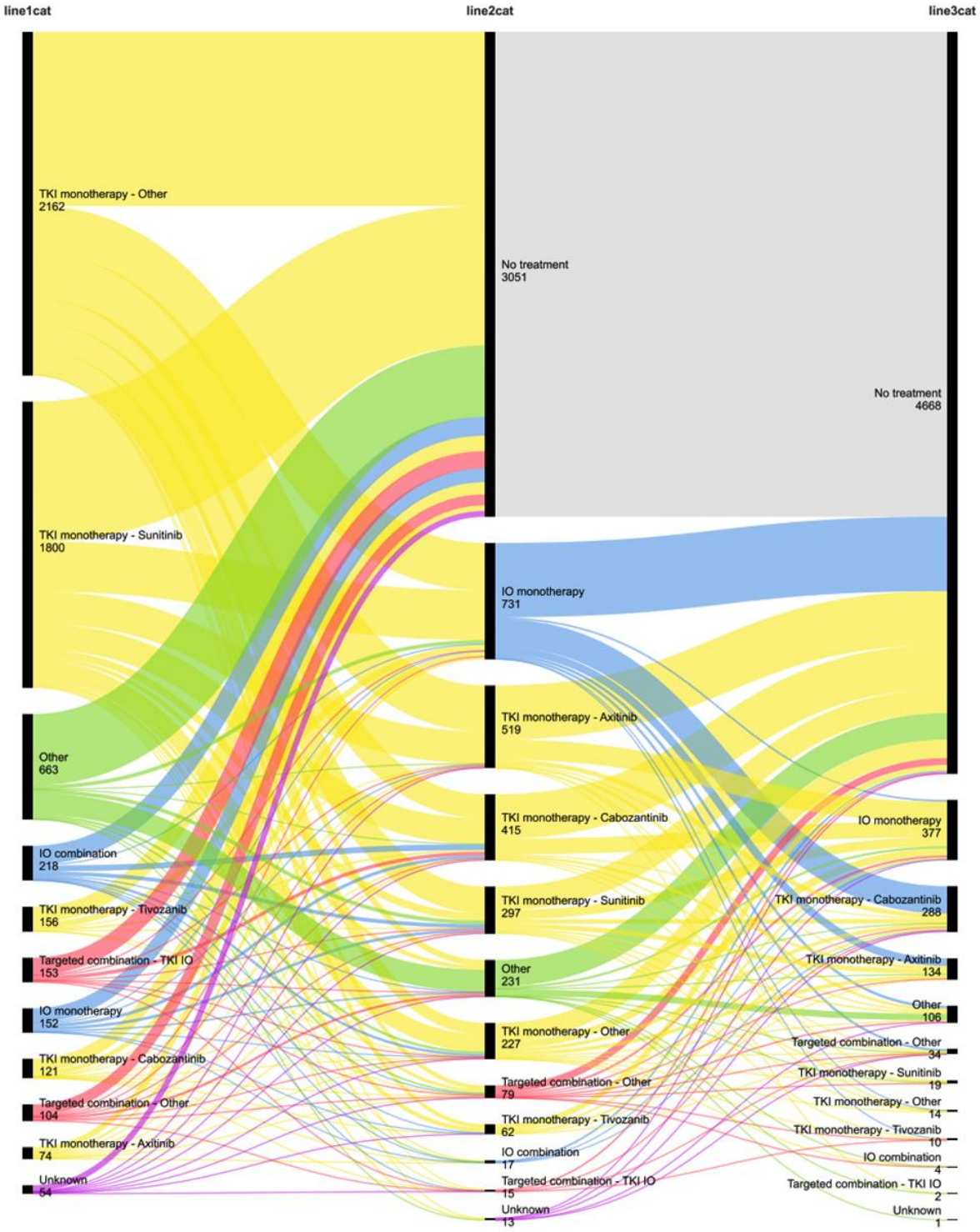
Treatment regimen	**Patients receiving systemic therapy (N = 5,657)**
First-line systemic treatment (Five most common categories)	**n = 5,282**
TKI monotherapy	**4,313 (76.2)**
Pazopanib	*2,125 (37.6)*
Sunitinib	*1,800 (31.8)*
Targeted combination	**257 (4.5)**
Avelumab + axitinib	*111 (2.0)*
IO combination	**218 (3.9)**
Nivolumab + ipilimumab	*103 (1.8)*
IO monotherapy	**152 (2.7)**
Nivolumab	*90 (1.6)*
mTORi monotherapy	***27 (0.5)***
Second-line systemic treatment (Five most common categories)	**n = 2,606**
TKI monotherapy	**1,520 (58.3)**
Axitinib	*519 (19.9)*
Cabozantinib	*415 (15.9)*
IO monotherapy	**731 (28.1)**
Nivolumab	*654 (25.1)*
Targeted combination	**94 (4.6)**
mTORi monotherapy	**60 (2.3)**
IO combination	**17 (0.7)**
Third-line systemic treatment (Five most common categories)	**n = 989**
TKI monotherapy	**465 (47.0)**

Treatment regimen	**Patients receiving systemic therapy (N = 5,657)**
Cabozantinib	*288 (29.1)*
Axitinib	*134 (13.5)*
IO monotherapy	**377 (38.1)**
Nivolumab	*357 (36.1)*
mTORi monotherapy	**45 (4.6)**
Targeted combination	**36 (3.6)**
Other targeted monotherapy	**11 (1.1)**

IO = immuno-oncology; mTORi = mechanistic target of rapamycin inhibitor TKI = tyrosine kinase inhibitor

FIGURES

Figure 1. Sankey diagram representing the treatment patterns among the overall cohort receiving systemic therapy



Note: TKI other includes 2,125 patients receiving pazopanib

Figure. 2. Factors associated with first-line treatment discontinuation.

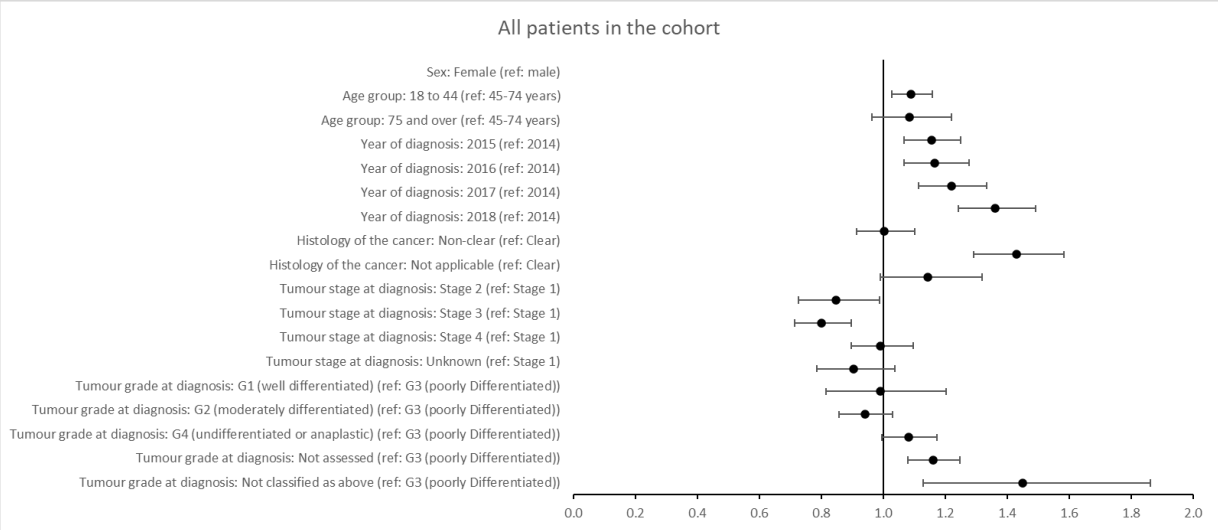
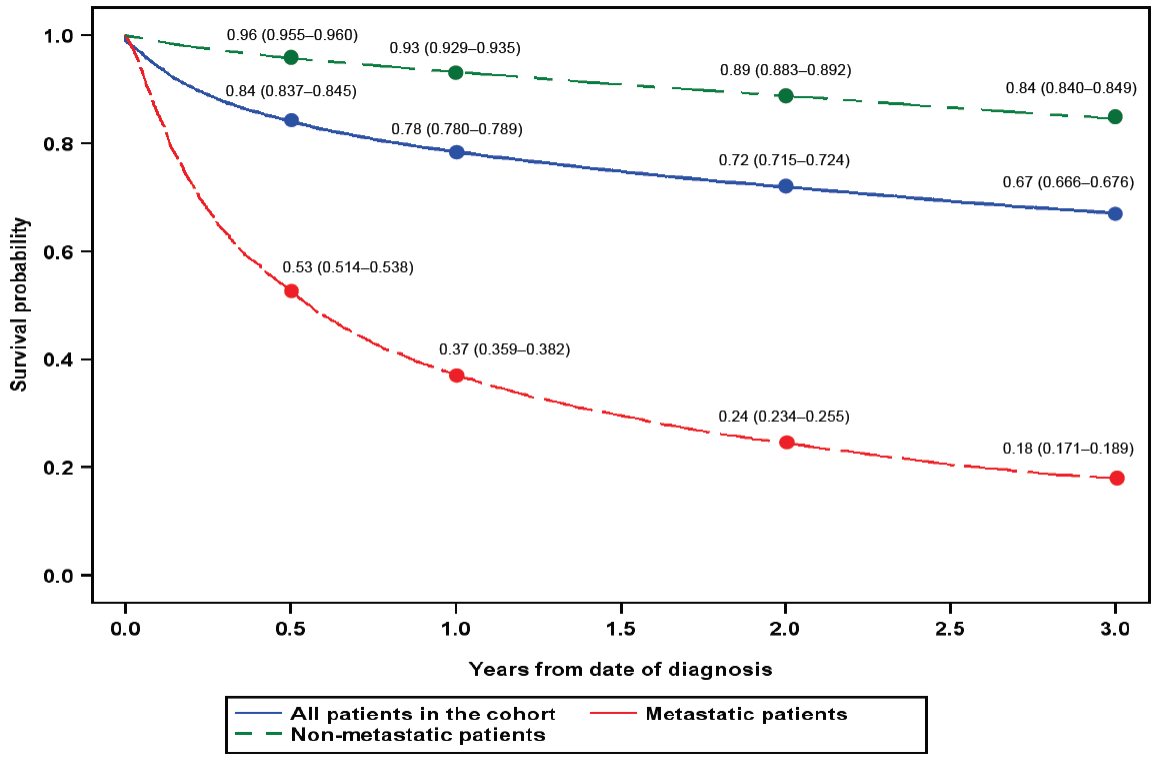


Figure 3. Overall survival from the date of diagnosis



SUPPLEMENTARY

Table A1. Codes used to identify patients with RCC

ICD-O3 Codes	Description
8312/3	Renal cell adenocarcinoma
8312/3	Renal cell carcinoma, NOS
8317/3	Chromophobe renal cell carcinoma
8316/3	Cyst-associated renal cell carcinoma
8260/3	Papillary renal cell carcinoma
8318/3	Sarcomatoid renal cell carcinoma
8318/3	Spindle cell renal cell carcinoma
8317/3	Chromophobe cell renal carcinoma
8319/3	Collecting duct type renal carcinoma
8041/3	Renal, reserve cell carcinoma

ICD-O3 = International Classification of Diseases for Oncology, Third Edition; NOS = not otherwise specified

Figure. A1. Adjusted Hazard Ratios for Factors Associated with Overall Survival ïamong patients with non-metastatic or metastatic disease at diagnosis