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Factors Associated With Prescription of Systemic Therapy in Real-world Patients With Metastatic Renal Cell Cancer Managed in a Rural Region

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Abstract. *Background/Aim: Numerous new treatment options have been approved for metastatic renal cell carcinoma (mRCC) in the last decade. Nevertheless, not all patients receive systemic therapy. Certain patients present with very advanced disease, poor Eastern Cooperative Oncology Group performance status (ECOG PS), or severe comorbidity, i.e. factors that lead oncologists to prefer best supportive care (BSC) instead of systemic therapy. The aim of this quality-of-care study was to identify baseline factors (disparities) associated with receipt of systemic therapy rather than BSC. Patients and Methods: This retrospective analysis included 140 consecutive patients managed in a rural region of Norway (2007-2022). Two differently managed groups were compared in univariate tests followed by multi-nominal regression. Results: The majority of patients (n=95, 68%) had received systemic therapy. Typical patients were males in their 60s or 70s, with clear cell histology, prior nephrectomy, and intermediate prognostic features. Patients who received systemic therapy lived significantly longer than those who did not (median 30.4 versus 5.0 months, p<0.001). Survival benefit of systemic treatment was observed even in patients with ECOG PS3 or age ≥80 years. In addition to younger age (p<0.001) and better ECOG PS (p<0.001), metachronous presentation was associated with higher rates of systemic therapy utilization (p=0.03). Conclusion: Assignment to systemic therapy for mRCC was individualized in the present patient population. In all age and ECOG PS subgroups, systemic therapy was associated with better survival (doubling at least). Optimum utilization rates are difficult to determine. However, in light of the survival outcomes, a rate of 12% in patients aged 80 years or older appears rather low.*

Metastatic renal cell carcinoma (mRCC) has developed from a devastating disease with limited treatment options to one of the success stories of modern oncology (1, 2). For almost 20 years, the therapeutic armamentarium has evolved after the introduction of the first tyrosine kinase inhibitors (TKI), which target vascular endothelial growth factor receptors (VEGFR), mammalian target of rapamycin (mTOR) and other pathways (3, 4). More recently, immune checkpoint inhibitors (ICI), such as nivolumab, ipilimumab and pembrolizumab have contributed to further improvement of outcomes. Combined treatment (ICI doublet or ICI plus TKI) has been identified as promising first-line systemic treatment approach (5-8). In selected patients, cytoreductive nephrectomy, metastasectomy, or stereotactic ablative radiotherapy may be considered, either up-front or delayed (9, 10). Furthermore, additional benefit may be expected from sequential administration of several lines of systemic therapy (11, 12).

Disparities may limit access to state-of-the-art systemic therapy, depending on health care system and other factors. Racial and ethnic minority patients and those living remotely from oncology facilities are less likely to receive certain types of treatment, a finding repeatedly shown in many cancer types including but not limited to mRCC (13, 14). Rural cancer care

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faces several challenges, *e.g.*, travel distance and socioeconomic differences between urban and rural populations (15-18). Under certain circumstances, withholding systemic therapy and putting the focus on best supportive care (BSC) is appropriate, depending on patient preferences, age, comorbidity, and performance status (PS). In other words, a realistic judgement of the risk/benefit-ratio is crucial. As a result of these considerations, we performed a retrospective quality-of-care study addressing receipt of systemic therapy *versus* BSC. Baseline parameters, such as age, disease extent and presentation were compared between the two groups (systemic therapy *versus* none). The setting of this study was a sparsely populated rural county in northern Norway where all oncologists are located at a single public hospital (Nordland Hospital in Bodø, the region's main hospital) and smaller local hospitals provide a defined range of basic services.

Patients and Methods

Patients. All study patients were covered by the publicly-funded Norwegian health care system and received treatment according to the national guidelines. The hospital's electronic patient records were employed to identify all patients with mRCC managed between 2007 and 2022, thereby expanding a previously utilized database (19). Baseline characteristics (patient- and disease-related), treatment (including previous nephrectomy) and date of death or last contact were abstracted. Prognosis was assessed retrospectively according to the Memorial Sloan Kettering Cancer Center (MSKCC) model, which includes PS, time interval, serum hemoglobin, calcium and lactate dehydrogenase (LDH) (20). In later years, the Heng *et al*. model was employed in addition, which features platelet and neutrophil counts, but not LDH (21).

Methods. Actuarial overall survival was calculated (Kaplan-Meier method) and compared between different groups with the log-rank test. The date of the radiological diagnosis of mRCC was defined as start date. Twenty-two patients were censored at the date of last contact after a median follow-up of 35.5 months (minimum 8 months). Date of death was recorded in all remaining 118 patients. Blood test results also relate to the date of the radiological diagnosis of mRCC. Two groups of patients were compared, who did or did not receive systemic therapy for mRCC. Baseline factors associated with receipt of systemic therapy were assessed with two-tailed Fisher exact probability tests or chi-square tests, followed by multi-nominal logistic regression. Statistical analyses were performed with IBM SPSS Statistics 29 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics. The majority of patients (n=95, 68%) had received systemic therapy. Of these, 50 had received at least two and 28 at least three different lines (22 patients under continuous care with potential to add further lines). Table I shows the different treatment approaches. As shown in Table II, typical patients were males 60 or 70 years old, with clear cell histology, prior nephrectomy, and intermediate prognostic features. Simultaneous presentation (metastases at first cancer diagnosis) was a common scenario (52%).

Table I. *Systemic therapy regimens*.

Drug regimen	Utilization in 1st line	Utilization in 2nd line	Utilization in 3rd line
Sunitinib	53	8	1
Pazopanib	22	11	1
Sorafenib	0	3	1
Axitinib	0	5	5
Cabozantinib	0	6	8
Everolimus	0	14	6
Temsirolimus	3	0	0
Bevacizumab/Interferon	5	0	0
Nivolumab	3	3	6
Ipilimumab/Nivolumab	6	0	0
Cabozantinib/Nivolumab	3	0	0

N: Number of patients.

Utilization of systemic therapy. The baseline parameters in Table II were analyzed with regard to different rates of systemic therapy utilization. Univariate correlations are shown in Table III. Age and Eastern Cooperative Oncology Group (ECOG) PS emerged as the most relevant predictors of systemic therapy utilization. All parameters shown in Table III were also analyzed in a multi-nominal logistic regression analysis, except for the Heng *et al*. prognostic model, which was undocumented in many patients. In addition to younger age ($p<0.001$) and better ECOG PS ($p<0.001$), metachronous presentation was associated with higher rates of systemic therapy utilization ($p=0.03$). Prognostic group was no longer significant.

Survival. Patients who received systemic therapy lived significantly longer than those who did not (median 30.4 *versus* 5.0 months, $p<0.001$, Figure 1). Median survival with systemic therapy was at least doubled in all MSKCC classes, throughout all ECOG PS groups, three age groups (all patients <60 years of age received systemic therapy), two Heng *et al*. prognostic classes (all patients in the good class received systemic therapy), and regardless of presentation (synchronous *versus* metachronous).

Discussion

This retrospective study in rural northern Norway assessed the receipt of systemic therapy in 140 real-world patients with mRCC. Typical patients were in their 60s or 70s, had clear cell histology and intermediate prognostic features. Ninety-five patients (68%) received any systemic therapy, most often sunitinib, but treatment recommendations evolved

Table II. *Baseline characteristics at the time of diagnosis of metastatic renal cell cancer.*

Characteristic	No	%
ECOG performance status (undocumented: 1)		
0	27	19
1	53	38
2	45	32
3	14	10
Sex		
Male	96	69
Female	44	31
Age		
<60 years	19	14
60-69 years	51	36
70-79 years	53	38
>79 years	17	12
Primary tumor histology		
Clear cell	124	89
Papillary	9	6
Others	7	5
Nephrectomy		
No	41	29
Yes	99	71
Interval between first cancer diagnosis and metastases		
Simultaneous	73	52
Metachronous within 1 year	27	19
1-5 years	19	14
More than 5 years	21	15
Metastatic sites		
Lung	92	66
Bone	53	38
Lymph node	55	39
Brain	23	16
Liver	29	21
Adrenal gland	27	19
Selected comorbid conditions		
Diabetes mellitus	22	16
Cardiac and/or vascular conditions	68	49
Memorial Sloan Kettering Cancer Center score (19)		
Good prognosis	23	16
Intermediate prognosis	83	59
Poor prognosis	31	22
Undocumented	3	2
Heng *et al*. score (20)		
Good prognosis	12	9
Intermediate prognosis	55	39
Poor prognosis	29	21
Undocumented	44	31

ECOG: Eastern Cooperative Oncology Group; N: number of patients.

Table III. *Predictors of utilization of systemic therapy.*

Characteristic	Percent systemic therapy	*p*-Value, univariate
Presentation		
Simultaneous	60	
Metachronous	76	0.049
Age		
<60 years	100	
60-69 years	82	
70-79 years	60	
>79 years	12	<0.001
Bone metastases		
Present	53	
Absent	79	0.002
Prior nephrectomy		
No	56	
Yes	73	0.07
ECOG performance status		
0	96	
1	74	
2	60	
3	14	<0.001
Memorial Sloan Kettering Cancer Center score (19)		
Good prognosis	78	
Intermediate prognosis	72	
Poor prognosis	48	0.03
Heng *et al*. score (20)		
Good prognosis	100	
Intermediate prognosis	76	
Poor prognosis	59	0.02

N: Number of patients; ECOG: Eastern Cooperative Oncology Group. Parameters with *p*-value >0.1 are not displayed.

as the publicly-funded health care system started funding of new drugs and recently also TKI/ICI combinations. National guidelines and drug price negotiations informed oncologists' choice of treatment. A small subgroup of patients started systemic therapy after initial active surveillance or local treatments, such as metastasectomy or radiotherapy. Even patients managed without systemic therapy have a certain, but low chance of long-term survival (Figure 1), illustrating the sometimes indolent course of mRCC. However, median survival was limited to 5.0 months, as compared to 30.4 months in patients who received systemic therapy. Regarding the 2nd and 3rd line utilization data, one should remember that 22 patients potentially will proceed to further treatment during follow-up.

We found that, in addition to younger age ($p<0.001$) and better ECOG PS ($p<0.001$), metachronous presentation was associated with higher rates of systemic therapy utilization ($p=0.03$). Memorial Sloan Kettering Cancer Center (MSKCC) prognostic group was not significant when analyzed together with age, ECOG PS and presentation. Metachronous presentation may indicate a less aggressive course of disease and also lower tumor burden, compared to many cases with synchronous presentation. Regardless of ECOG PS, age group, presentation, and prognostic class, systemic therapy was always associated with clearly improved survival, indicating that our oncologists succeeded

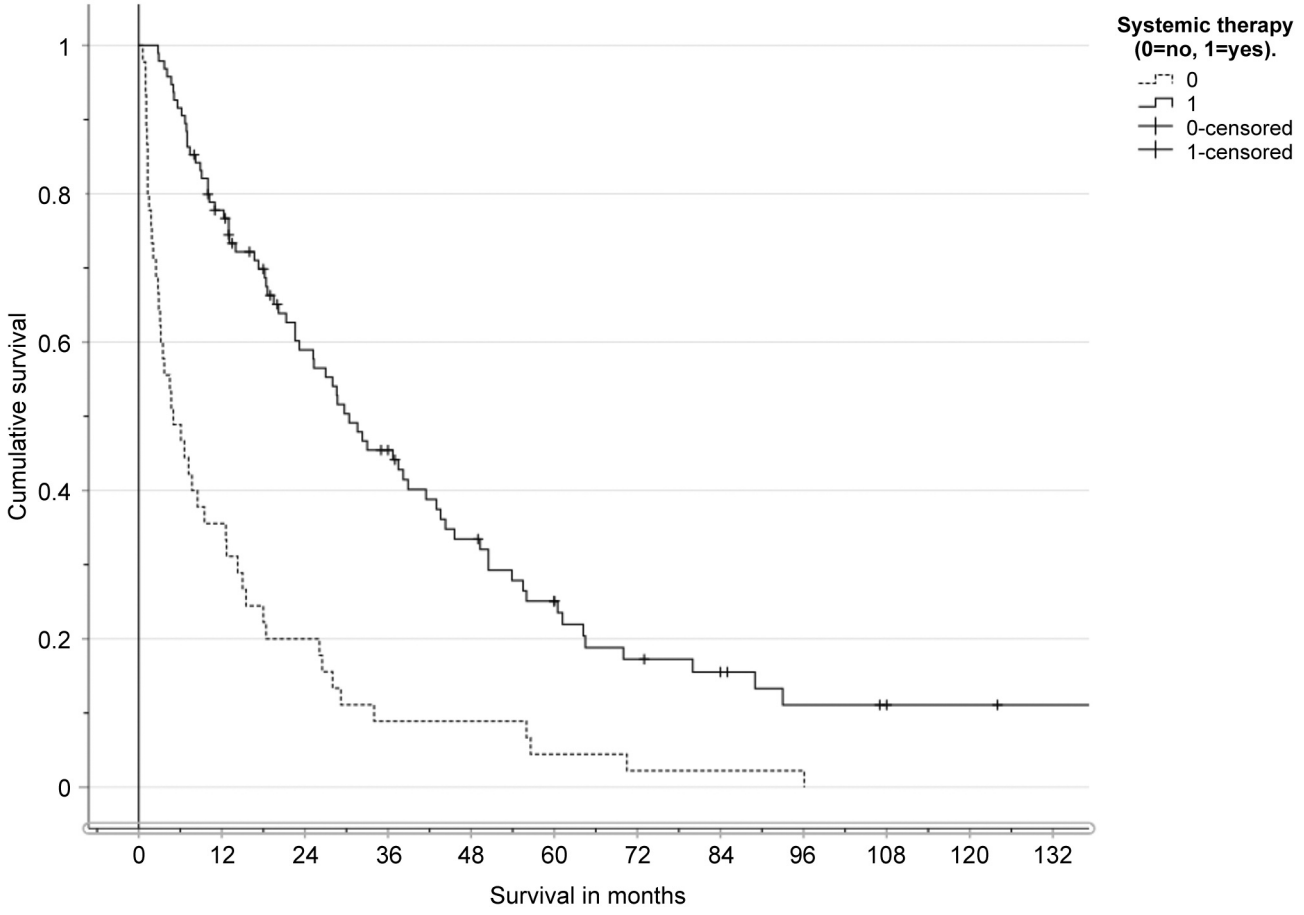

Figure 1. *Actuarial overall survival in patients who did (n=95) or did not (n=45) receive systemic therapy, median 30.4 and 5.0 months, respectively, p<0.001.*

in selecting appropriate patients. Only 8 patients (8%) of those who started systemic therapy died within 6 months. On the other hand, it is difficult to judge whether or not some of the patients who did not receive systemic therapy may have benefited from such treatment. In other words, there is no generally agreed optimum utilization rate. The final decision should be made together with the patient and caregivers, taking individual preferences and goals of care into account, after careful judgement of risks and benefits. Undoubtedly, a subgroup of patients exists which qualifies for BSC, *e.g.*, due to very old age and high comorbidity burden, or extremely advanced disease and reduced ECOG PS. Ideally, dedicated prospective studies would analyze borderline cases to confirm that a real benefit from systemic therapy exists and that treatment is safe. At present, an unprecedentedly large number of first-line options with different toxicity profiles is available (1, 11, 22).

When interpreting our results, several limitations in the study design should be taken into consideration, *e.g.*, retrospective single-institution analysis and limited number of patients. The latter also explains why we did not stratify for different reasons leading to a decision against systemic therapy (patient refusal, oncologist recommendation, preference of other treatment options such as palliative radiotherapy, *etc.*). In contrast to a prospective study with early assignment to a specific treatment arm (intention-to-treat), it is possible that in our retrospective setting some patients who were planned for systemic therapy actually did not receive it, because of rapid deterioration or serious acute events related to comorbidity. Furthermore, some patients may not have been referred to an oncologist, meaning that additional BSC patients may have gone unidentified.

A different Norwegian study covering the years 2002-11 showed that 63% of patients received systemic TKI in the time period 2009-2011 (23). The proportion of patients who did not receive any systemic therapy decreased steadily from 94% in 2002 to 28% in 2011 (32% in our study, 2007-2022). Age was higher in untreated patients. Overall, mRCC patients who received at least one targeted therapy had a significantly reduced risk of death *versus* those who did not

receive targeted therapy (HR=0.57; 95% confidence interval=0.51-0.65; $p<0.001$), with median survival of 17.0 and 8.0 months, respectively.

Other researchers analyzed patients diagnosed with mRCC in the National Cancer Database (2004-2015; USA) (24). In this setting, 26% of patients received no treatment. The authors identified racial, sex, and socioeconomic differences in the treatment of mRCC which were associated with a disparity in overall survival. Females were at lower odds of receiving systemic therapy (odds ratio=0.91, $p<0.01$) and increased odds of no treatment, in contrast to our Norwegian data. Also in US Medicare beneficiaries from 2015 to 2019 disparities by race, ethnicity, and sex were observed in mRCC systemic therapy utilization (25). A third group used Surveillance, Epidemiology, and End Results (SEER)Medicare data to identify patients ≥65 years of age who were diagnosed with mRCC from 2007 to 2015 and enrolled in Medicare Part D (26). Insurance claims were used to identify receipt of oral mRCC drugs within 12 months of metastatic diagnosis. Provider and hospital factors, specifically, being seen by a medical oncologist for mRCC diagnosis, were associated with treatment initiation. Older patients >81 years of age were less likely to see a medical oncologist. Probably, some of these older patients were not referred because of fear of poor treatment tolerance and reduced quality-of-life. Notable differences exist between the US and the less heterogeneous, publicly-funded Norwegian health care system (27, 28), hampering international comparison.

Conclusion

Assignment to systemic therapy for mRCC was individualized in the present patient population. In all age and ECOG PS subgroups, systemic therapy was associated with better survival (doubling at least). Optimum utilization rates are difficult to determine. However, in light of survival outcomes, a rate of 12% in patients aged 80 years or older appears rather low.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. CN, LS and ECH conceived the study and drafted the article. All Authors read and approved the final article.

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