Changes in treatment patterns and survival in Renal Cell Carcinoma patients in Norway – A nationwide registry study for 1995-2018

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Background

In Norway, cancer treatment is publicly funded, allowing equal care to all patients. Mandatory nationwide population registries capture data on diagnoses, treatments and comorbidities. This enabled us to retrieve data for this longitudinal retrospective study and describe clinical and demographic characteristics, treatment patterns and survival of patients with renal cell carcinoma (RCC).

Study objectives

Primary objective of our study is to describe clinical outcomes for patients with RCC and advanced RCC (mRCC), including overall survival (OS), by factors of disease stage, histology, drug utilization patterns (i.e., number of therapy lines, sequence), temporal trends, co-morbidity load, age and gender. **Secondary objectives** include detailed analysis of management for RCC and mRCC; nephrectomy, radiation, systemic therapy lines, combination, sequence, and switch patterns of drug therapies and the analysis of the health care resource utilization and direct costs associated with RCC and mRCC management.

Here we present the most important results from the survival and systemic treatment data analysis.

Methods

The source population was selected using the Cancer Registry of Norway (CNR) and included all adult patients with any grade RCC diagnosed (using ICD10 and histology codes) in the period 1995-2018. The CRN source population was linked with longitudinal data from the Norwegian Prescription Database, the Norwegian Patient Register (NPR), the Norwegian Primary Care Register. Follow-up period was extended until 30 June 2019 allowing a minimum of 6 months of follow-up on all patients. Statistical analysis was performed by Kaplan-Meier method and Cox multivariate regression models.

Results

Population

Overall, 12,767 patients were diagnosed with RCC during the whole studied period and 4,150 had advanced disease (mRCC). Population characteristics are shown **Table 1.**

	RCC N=8,617	mRCC N= 4,150	Overall N=12,767
Gender, N (%)			
Female	3064 (35.6)	1264 (30.5)	4328 (33.9)
Male	5553 (64.4)	2886 (69.5)	8439 (66.1)
Age at diagnosis, N (%)			
≤49	153 (13.4)	372 (9.0)	1525 (11.9)
50-59	1697 (19.7)	851 (20.5)	2548 (20.0)
60-69	2547 (29.6)	1271 (30.6)	3818 (29.9)
70-79	2452 (28.5)	1254 (30.2)	3706 (29.0)
≥80	768 (8.9)	402 (9.7)	1170 (9.2)
Histology			
Clear cell	6581 (76.4)	3382 (81.5)	9962 (78.0)
Chromophobe	434 (5.0)	83 (2.0)	571 (4.0)
Papillary	1250 (14.5)	334 (8.0)	1584 (12.4)
Other	352 (4.1)	352 (8.5)	705 (5.5)
Surgery			
Partial nephrectomy	2231 (25.9)	261 (6.3)	2492 (19.5)
Total nephrectomy	5972 (69.3)	2568 (61.9)	8540 (66.9)
Death during follow-up			
No	5790 (67.2)	947 (22.8)	6737 (52.8)
Yes	2827 (32.8)	3203 (77.2)	6030 (47.2)
Death due to RCC			
No	7790 (90.4)	1798 (43.3)	9588 (75.1)
Yes	827 (9.6)	2352 (56.7)	3179 (24.9)

Table 1. Population characteristics of RCC patients in Norway diagnosed in the period 1995-2018

Survival analysis

Median overall survival was 9.3 and 1.2 years in the whole RCC and mRCC cohort, respectively, with an incrementally improving OS between 1995 and 2018 **(Figure 1).**

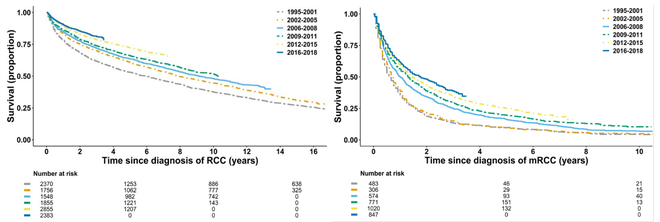

Figure 1. Median overall survival **a)** RCC cohort **b)** mRCC cohort, both stratified by year of diagnosis

Factors related to shorter survival were diagnosis of metastatic disease, older age and earlier calendar year at diagnosis in all patients, and Charlson`s comorbidity score ≥ 2 in patients with RCC, but not in patients with metastatic disease.

Survival according to number of therapy lines

Of 3,072 patients diagnosed with mRCC after 1 January 2008, 1,537 received at least one line of systemic therapy. Of those, 43% received only one line of therapy, 27% two lines, 15% three - and the remainder four or more therapy lines, with no changes between 2008 and 2019 **(Table 2)**.

Year, N / Number of treatment lines, N (%)	2008-2009 N=229	2010-2011 N=281	2012-2013 N=255	2014-2015 N=295	2016-2017 N=287	2018-2019 N=190	Overall N=1537
1	106 (46%)	125 (44%)	97 (38%)	125 (42%)	119 (41%)	95 (49%)	666 (43%)
2	58 (25%)	72 (26%)	73 (29%)	66 (22%)	85 (30%)	55 (30%)	409 (27%)
3	30 (13%)	36 (13%)	39 (15%)	46 (16%)	48 (17%)	32 (17%)	231 (15 %)
4	18 (8%)	23 (8%)	29 (11%)	25 (8%)	17 (6%)	6 (3%)	118 (8%)
5	6 (3%)	9 (3%)	9 (4%)	24 (8%)	12 (4%)	1 (0.5%)	61 (4%)
6	6 (3%)	11 (4%)	6 (2%)	2 (1%)	4 (1%)	1 (0.5%)	28 (1,5%)
≥7	5 (2%)	5 (2%)	2 (1%)	7 (3%)	3 (1%)	0 (0%)	24 (1.5%)

Table 2. Patients with mRCC and number of lines of systemic therapy, stratified by calendar year of mRCC diagnosis

Increasing number of therapy lines was related to longer median OS, 1.0, 1.6 and 2.6 years, respectively, for patients receiving one, two or three therapy lines **(Figure 2)**.

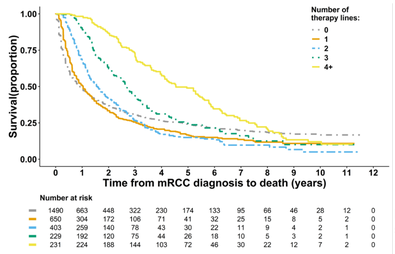

Figure 2. Kaplan-Meier analysis of survival according to number of therapy lines

Tyrosine kinase inhibitors (TKIs) were commonly used in first line, while use of mammalian target of rapamycin (mTOR) inhibitor decreased over time and was replaced with immunotherapy (IO) and TKIs in subsequent lines.

Therapy sequencing and significant survival benefit in patients treated with immunotherapy

Differences in survival according to therapy sequence in 401 patients with mRCC who received three or more therapy lines is shown in **Figure 3**. Patients that received IO as a part of their treatment had significantly longer median overall survival of 4.7 years compared to 2.5 years in patients never receiving IO (HR 0.28, 95%CI 0.19-0.41). The magnitude of this difference was surprisingly high, keeping in mind that IO therapy in this cohort was almost exclusively Nivolumab in the second or third line of treatment. Survival difference between IO and non-IO cohort was even more pronounced in multivariate analysis and could not be explained neither by response to IO nor duration of treatment in each therapy line.

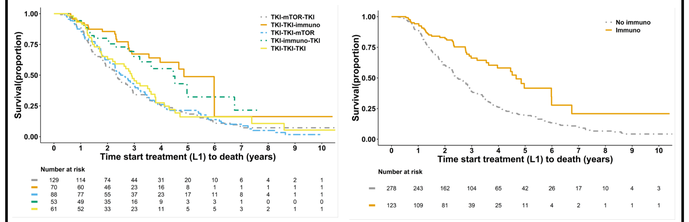

Figure 3. Kaplan-Meier analysis of survival **a)** according to therapy sequence from start of first treatment to death, **b)** use of immunotherapy

Conclusion

This study represents a complete population-wide analysis of RCC patients in Norway over a period of 23 years, providing comprehensive real-world evidence on treatment and survival before and after introduction of new therapies. The results are in line with survival benefits reported in clinical trials and warrant use of modern therapies in daily clinical practice, especially immunotherapy seems to play important role in survival benefit.

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- First author has following financial interests to declare:
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