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Improved overall survival after implementation of targeted therapy for patients with metastatic renal cell carcinoma: Results from the Danish Renal Cancer Group (DARENCA) study-2

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Abstract ***Aim:*** To evaluate the implementation of targeted therapy on overall survival (OS) in a complete national cohort of patients with metastatic renal cell carcinoma (mRCC).
Methods: All Danish patients with mRCC referred for first line treatment with immunotherapy, TKIs or mTOR-inhibitors between 2006 and 2010 were included. Baseline and outcome data were collected retrospectively. Prognostics factors were identified using log-rank tests and Cox proportional hazard model. Differences in distributions were tested with the Chi-square test.
Results: 1049 patients were referred; 744 patients received first line treatment. From 2006 to 2010 we observed a significant increase in the number of referred patients; a significant increase in treated patients (64% versus 75%, $P = 0.0188$); a significant increase in first line targeted therapy (22% versus 75%, $P < 0.0001$); a significant increase in second line treatment (20% versus 40%, $P = 0.0104$), a significant increased median OS (11.5 versus 17.2 months, $P = 0.0435$) whereas survival for untreated patients remained unchanged. Multivariate analysis validated known prognostic factors. Moreover, treatment start years 2008 (HR 0.74, 95% CI, 0.55–0.99; $P = 0.0415$), 2009 (HR 0.72, 95% CI, 0.54–0.96; $P = 0.0277$) and 2010

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(HR 0.63, 95% CI, 0.47–0.86; $P = 0.0035$) compared to 2006, and more than two treatment lines received for patients with performance status 0–1 (HR 0.76, 95% CI, 0.58–0.99; $P = 0.0397$) and performance status 2–3 (HR 0.19, 95% CI, 0.06–0.60; $P = 0.0051$) were significantly associated with longer OS.

Conclusion: This retrospective study documents that the implementation of targeted therapy has resulted in significantly improved treatment rates and overall survival in a complete national cohort of treated mRCC patients.

1. Introduction

Prior to the introduction of targeted therapy with tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin (mTOR) inhibitors, treatment options for patients with metastatic renal cell carcinoma (mRCC) were limited. Chemotherapy did not impact overall survival (OS) and immunotherapy was only given to patients in good performance status (PS). The introduction of targeted therapy has therefore expanded treatment opportunities. In Denmark, sorafenib became available in 2006 [1], sunitinib [2] and temsirolimus [3] in 2007, everolimus [4] in 2009, pazopanib [5] in 2010 and axitinib in 2013. These new drugs were approved due to significant improvements in progression free survival (PFS), but only temsirolimus has demonstrated a statistically significant improved OS in poor risk mRCC patients [3].

Cancer treatment in Denmark is free with equal access to surgery, systemic therapy and palliative care. Treatment of mRCC is restricted to four centres; there are no private clinics for systemic cancer treatment. All Danish citizens are assigned a unique social security number at birth or immigration and all contacts with the health system are based on this number. It is therefore possible to track all patients from diagnosis until date of death. This gives a unique opportunity to identify and study a complete national cohort of treated patients with mRCC and an untreated cohort.

This study assessed the first 5 years of the implementation of targeted therapy in a complete national cohort of treated patients with mRCC to investigate whether OS was improved in real-life settings.

2. Patients and methods

2.1. Patient characteristics

Medical oncology treatment for mRCC was centralised at four hospitals in Denmark (Aarhus University Hospital, Odense University Hospital, University Hospital of Copenhagen Rigshospitalet, and the University Hospital of Copenhagen Herlev). All patients with biopsy-proven mRCC referred for medical oncology treatment between January 1st 2006 and December 31st 2010 were identified by a National Registry (GS-Open) and institution databases. Individual medical records were collected and reviewed. All patients, who started first line treatment with immunotherapy, TKIs, or mTOR-inhibitors for mRCC, were included. Baseline clinical and paraclinical data were collected retrospectively. Blood samples were standardised to the treating hospital's Upper Level of Normal (ULN) and Lower Level of Normal (LLN). A central pathology review was performed by a single pathologist to ensure histological subtype. Subtyping was done according to the WHO 2004 classification. Patients were excluded if their diagnosis of renal cell carcinoma (RCC) was unconfirmed. Untreated patients with locally advanced or metastatic disease, referred for systemic treatment were also registered. Data on patients with mRCC not referred for oncological treatment were not available.

2.2. Treatment regimens

Treatment options included sunitinib, sorafenib, temsirolimus, everolimus, subcutaneous interferon-α or interleukin-2 in combination with interferon-α, or protocol treatment with dendritic cell vaccination, sorafenib, subcutaneous interleukin-21, subcutaneous interferon-α ± subcutaneous interleukin-2 and fluorouracil or subcutaneous interleukin-2 in combination with interferon-α ± bevacizumab. Treatment choice was decided by the local treating physician according to national guidelines. Standard treatments were given with standard dosing and schedules according to regulatory approvals. Trial results from treatment with interleukin-21, sorafenib, dendritic cell vaccination, interferon-α ± interleukin-2 and fluorouracil have been published previously [6–9].

2.3. Statistical analysis

OS was defined as time from first day of each treatment line until death of any cause and analysed according to validated prognostic factors [10,11], number of treatment lines received and year of treatment start. OS for untreated patients was calculated from the date of metastatic disease until the date of death. Patients alive at the end of study or emigrated were censored (last follow up was 2012-10-31). PFS was not analysed due to lack of central radiological review. Time to treatment failure (TTF) was defined from the first day on each treatment line until the date of treatment discontinuation due to adverse events, patients request, locally

assessed progression, death or other reasons. For patients completing the scheduled immunotherapy treatment, TTF was registered at date of progression (assessed locally), death or beginning of a new treatment line. Patients were censored if they emigrated or were alive at the end of study (2010-12-31). OS and TTF were calculated using the Kaplan–Meier method and median follow up time with the reverse Kaplan–Meier method. Differences in distributions were tested with the Chi-square test. Missing values were handled with case-deletion method. Association between prognostic factors, treatment start year, number of treatment lines received and OS were tested with log-rank test and a significance level of $P \leqslant 0.05$ was chosen as an entry point for the multivariate analysis using Cox proportional hazards model. Statistical analyses were performed using R version 2.14.0. (2011 The R Foundation for Statistical Computing).

2.4. Ethics

The study was approved by the Danish Health Authorities, the Danish Research Ethics Committee and the Danish Data Protection Agency. The study was registered with ClinicalTrials.gov NCT01339962.

3. Results

3.1. Patient characteristics

Overall, 1049 patients were identified of which 744 patients received first line treatment from 2006 to 2010. Seven-hundred-and-fifty-nine patients received first line treatment but 15 (2%) patients were excluded after the central pathology review due to a diagnosis other than RCC. Patient characteristics of the 744 patients are listed in Table 1.

Three-hundred-and-seven (41%) patients received immunotherapy and 437 (59%) received targeted therapy as first line treatment. Five-hundred-and-eighty-seven (79%) patients had an Eastern Cooperative Oncology Group PS of 0–1. A total of 457 (61%) patients had undergone a nephrectomy of which 21 (3%) patients underwent nephrectomy following first line treatment. The histological subtypes were clearcell (612 patients, 82%), chromofobe (16 patients, 2%), papillary type 1 (30 patients, 4%), papillary type 2 (39 patients, 5%), collecting ducts (6 patients, 1%), mucinous tubular and spindle cell (3 patients, <1%) and unclassified (27 patients, 4%). Specimens from 11 (1%) patients could not be retrieved. The distribution of patients according to Hengs classification showed a high proportion (39%) in the poor prognostic group. One-hundred-and-twenty-nine (17%) patients were still on treatment. Treatment was mainly discontinued due to progressive disease (41%), side-effects (11%), and decline in PS (10%).

The patient populations commencing therapy in 2006 and 2010 had no statistically different distribution of well-established prognostic factors, except more patients had presence of brain metastases in 2010 than 2006 (7% versus 2%) and fewer patients had elevated calcium in 2010 compared to 2006 (13% versus 46%).

3.2. Untreated patients

Three-hundred-and-five patients were referred but did not receive systemic treatment with only 11 (4%) patients being alive at last follow up and two (1%) patients emigrated (Supplementary Table 1). Forty-five (15%) patients had a PS of 0–1. It was not possible to estimate Hengs prognostic group for 99 patients (32%) mostly due to lack of blood samples, but there were as many as 183 (60%) patients in the poor prognosis group. Poor PS was the main reason for not receiving systemic treatment (171 patients, 56%) while patient request and death before treatment start accounted for 50 (16%) and 44 (14%) patients, respectively. The main reason for not receiving treatment for patients in Hengs good and intermediate risk groups was patient request (40%, data not shown).

3.3. Treatment regimens

The distribution of patients per year and per drug for first line treatment is listed in Table 2a. An increased number of patients was referred between 2006 and 2010 ($P = 0.0492$). The proportion of patients receiving first line treatment increased significantly from 64% in 2006 to 75% in 2010 ($P = 0.0188$). The proportion of patients receiving targeted therapy as first line treatment increased from 22% in 2006 to 75% in 2010 ($P < 0.0001$).

During the study period 273 (37%) of the 744 patients received second line treatment and 91 (12%), 29 (4%), 10 (1%) and 3 (<1%) patients received third, fourth, fifth and sixth line treatment, respectively (Table 2b). In 2006 20% patients received second line treatment compared to 40% patients in 2010 ($P = 0.0104$). Over the years, a higher proportion of patients received additional treatment lines. 50% of the patients who received second line treatment continued on third line treatment in 2010 compared to 13%, 40% and 39% in 2007, 2008 and 2009, respectively. There was a similar tendency over time for fourth, fifth and sixth line treatments although the patient numbers were low. Cytokines and sunitinib were the most preferred treatment choices in first line treatment followed by sorafenib and sunitinib in second and third line. Everolimus was predominantly used in third and fourth line and temsirolimus was rarely used (Supplementary Table 2).

Table 1
Characteristics of Danish patients treated for mRCC by the period of treatment.

Variable	First line 2006–2010	2006	2010	*P* value[a]
Total number of patients (%)	744 (100)	113 (100)	163 (100)	
Emigrated (%)	4 (1)	1 (1)	1 (1)	
Median age (IQR)	62 (57–69)	60 (53–67)	64 (58–71)	0.0779[b]
Sex (male, %)	514 (69)	80 (71)	114 (70)	0.8781
PS				0.3701[c]
0 (%)	295 (40)	41 (36)	70 (43)	
1 (%)	292 (39)	52 (46)	62 (38)	
2 (%)	126 (17)	15 (13)	24 (15)	
3 (%)	10 (1)	0 (0)	5 (3)	
NA (%)	21 (3)	5 (4)	2 (1)	
Median KPS (IQR)	90 (80–100)	90 (80–100)	90 (80–100)	
KPS NA (%)	33 (4)	10 (9)	2 (1)	
Heng				0.5348
Favourable (%)	79 (11)	13 (12)	25 (15)	
Intermediate (%)	367 (49)	50 (44)	78 (48)	
Poor (%)	289 (39)	47 (42)	60 (37)	
NA (%)	9 (1)	3 (3)	0 (0)	
Hgb < LLN (%)	366 (49)	58 (53)	85 (52)	0.925
NA (%)	3 (<1)	3 (3)	0 (0)	
LDH > 1.5 times ULN (%)	73 (10)	11 (10)	20 (13)	0.579
NA (%)	17 (2)	6 (5)	3 (2)	
Platelets > ULN (%)	208 (28)	20 (18)	43 (26)	0.1148
NA (%)	4 (1)	3 (3)	0 (0)	
Neutrophils > ULN (%)	225 (31)	29 (26)	50 (31)	0.441
NA (%)	8 (1)	3 (3)	0 (0)	
Ca^{2+} > ULN (%)	164 (23)	50 (46)	20 (13)	<0.0001
NA (%)	16 (2)	4 (4)	3 (2)	
Nephrectomy performed (%)	457 (61)	64 (56)	108 (66)	0.1048
Histology				0.8488
Clearcell (%)	612 (82)	90 (80)	134 (82)	
Non-clearcell (%)	121 (16)	20 (18)	28 (17)	
NA (%)	11 (1)	3 (3)	1 (1)	
Less than 1 year from diagnoses (%)	555 (75)	79 (70)	121 (74)	0.4293
CNS metastases present (%)	52 (7)	2 (2)	12 (7)	0.0374
Liver metastases present (%)	157 (21)	22 (19)	32 (20)	0.9732
Metastatic sites				0.2245
1–2 (%)	369 (50)	59 (52)	73 (45)	
More than 2 (%)	375 (50)	54 (48)	90 (55)	
First line treatment				
IL2/Interferon-alfa regimens (%)	304 (41)	86 (76)	40 (25)	
Dendritic cell vaccination (%)	3 (<1)	2 (2)	1 (1)	
Sorafenib (%)	67 (9)	24 (21)	4 (2)	
Sunitinib (%)	364 (49)	1 (1)	112 (69)	
Temsirolimus (%)	3 (<1)	0 (0)	3 (2)	
Everolimus (%)	3 (<1)	0 (0)	3 (2)	
Reason for treatment failure				
Progression (%)	306 (41)	65 (58)	33 (20)	
Death (%)	61 (8)	9 (8)	10 (6)	
Patient request (%)	47 (6)	9 (8)	9 (6)	
Side effects (%)	85 (11)	9 (8)	16 (10)	
Decline in performance status (%)	77 (10)	13 (12)	15 (9)	
Other (%)	39 (5)	5 (4)	2 (1)	

mRCC, metastatic renal cell carcinoma; IQR, interquartile range; PS, performance status; NA, not applicable; KPS, Karnofsky performance status; Hgb, haemoglobin; LLN, lower level of normal; LDH, lactate dehydrogenase; ULN, Upper Level of Normal; Blood samples below or above levels are given as a proportion of the available samples.

[a] Chi-square test between 2006 and 2010.

[b] For age of 63 years and above or below 63 years.

[c] For PS of 1 and below or above 1.

Table 2
(a) Drug distribution for first line treatment per year; (b) number of patient distributed on each treatment line per year, in Danish mRCC patients between 2006 and 2010.

	2006	2007	2008	2009	2010	2006–2010	*P* value
a.							
First line							
Immunotherapy (%)	88 (78)	64 (45)	69 (43)	45 (27)	41 (25)	307	
Cytokines	86	64	69	45	40	304	
Dendritic cell vaccination	2	0	0	0	1	3	
Targeted therapy (%)	25 (22)	77 (55)	93 (57)	120 (73)	122 (75)	437	<0.0001[a]
Everolimus	0	0	0	0	3	3	
Sorafenib	24	28	10	1	4	67	
Sunitinib	1	49	83	119	112	364	
Temsirolimus	0	0	0	0	3	3	
Untreated patients	64	74	59	55	53	305	
Total referred patients	177	215	221	220	216	1049	0.0492[a]
Treatment proportion	64%	66%	73%	75%	75%	71%	0.0188
	2006	2007	2008	2009	2010	2006–2010[b]	*P* value
b.							
First line (%)	113 (100)	141 (100)	162 (100)	165 (100)	163 (100)	744 (100)	
Second line (%)	23 (20)	56 (40)	52 (32)	76 (46)	66 (40)	273 (37)	0.0104[a]
Third line (%)	0 (0)	7 (13)	21 (40)	30 (39)	33 (50)	91 (12)	
Fourth line (%)	0 (0)	0 (0)	4 (19)	10 (33)	15 (45)	29 (4)	
Fifth line (%)	0 (0)	0 (0)	0 (0)	1 (10)	9 (60)	10 (1)	
Sixth line (%)	0 (0)	0 (0)	0 (0)	0 (0)	3 (33)	3 (<1)	

mRCC, metastatic renal cell carcinoma.
[a] Between 2006 and 2010.
[b] First line patients receiving additional treatment lines.

3.4. Survival analysis

One-hundred-and-thirty-seven (18%) patients were alive at last follow up. Four (1%) patients were censored due to emigration. Median follow up time for OS was 49.1 months (range: 2.0–81.8). Median OS for treated patients increased significantly from 11.5 months in 2006 to 17.2 months in 2010 ($P = 0.0435$; Table 3 and Fig. 1). Median OS for Hengs favourable, intermediate and poor risk groups were 33.4, 18.6 and 5.8 months, respectively. A significant improvement in median OS between 2006 and 2010 was observed for the favourable risk group (27.8 months versus not reached, $P = 0.045$). There were a tendency for improved OS in the intermediate risk group but it was not significant. Median OS was almost unchanged for the poor risk group (Fig. 2A–D). Median OS for untreated patients was 3.0 months (95% CI, 2.6–3.8) with no significant change from 2006 to 2010 ($P = 0.676$; Supplementary Table S3).

Median follow up time for TTF was 23.5 months (range: 0.1–55.1) and 129 (17%) patients were censored at the end of study. We observed the median TTF for first line treatment improved from 3.1 months (95% CI, 2.9–4.2) in 2006 to 4.9 months (95% CI, 3.8–6.4) in 2010 ($P = 0.0058$; Supplementary Table S3).

3.5. Univariate analysis

PS, prior nephrectomy, time from diagnose to treatment start, presence of CNS and liver metastases, treatment year 2006 compared to 2010, number of metastatic sites, histology, Hengs risk groups, haemoglobin, platelets, neutrophils, calcium and LDH were all indicators of OS (Table 3). Patients that received more than two treatment lines had a significantly longer OS from the start of first line treatment compared to patients that received 1–2 lines of treatment (27.8 versus 11.5 months, $P < 0.0001$).

3.6. Multivariate analysis

The multivariate analysis (Table 4) was based on 688 patients; 56 patients were deleted due to missing values. The model was corrected for interaction between PS and the number of treatment lines received. Haemoglobin below LLN, LDH 1.5 times above ULN, platelets and neutrophils above ULN, non-clearcell histology, less than 1 year from diagnose to treatment start and more than 2 metastatic sites were significantly associated with shorter OS for first line treatment. Hypercalcaemia was borderline significant. Patients who received more than two treatment lines had a longer OS compared to 1 or 2 treatment lines. Patients in PS 0–1 had a significant longer OS if they received 3–6 treatment lines compared to 1 or 2 treatment lines (HR 0.76, 95% CI, 0.58–0.99; $P = 0.0397$). Patients in PS 2–3 also had a significantly longer OS if they received 3–6 treatment lines compared to 1 or 2 treatment lines (HR 0.19, 95% CI, 0.06–0.60; $P = 0.0051$). Patients who received 1 or 2 treatment lines and were in PS 0–1 had a longer OS compared to

Table 3
Univariate analysis of predictors of overall survival for Danish patients treated for mRCC between 2006 and 2010.

Risk factor	*N*	%	% Alive	Median OS	95% CI	*P* value
Age						0.467
⩾63	390	52	18	14.1	11.7–15.7	
<63	354	48	20	13.8	11.5–17.7	
Gender						0.693
Male	514	69	20	13.5	11.5–15.3	
Female	230	31	17	15.3	12.6–18.4	
Heng						<0.0001
Favourable	79	11	46	33.4	29.4–44.7	
Intermediate	367	50	23	18.6	16.7–21.4	
Poor	289	39	6	5.8	5.0–7.2	
PS						<0.0001
0–1	587	81	22	17.2	15.3–19.2	
>1	136	19	6	4.0	3.1–5.8	
Received treatment lines						<0.0001
1–2	653	88	20	11.5	10.1–13.5	
3–6	91	12	14	27.8	25.7–33.1	
Haemoglobin						<0.0001
<LLN	366	49	10	8.2	7.1–10.0	
>LLN	375	51	28	23.2	20.1–26.9	
LDH						<0.0001
<1.5× ULN	654	90	22	16.1	14.3–18.0	
>1.5× ULN	73	10	0	3.6	3.1–4.5	
Platelets						<0.0001
<ULN	532	72	23	17.8	15.4–19.8	
>ULN	208	28	8	8.1	6.7–10.6	
Neutrophils						<0.0001
<ULN	511	69	25	18.1	16.3–20.4	
>ULN	225	31	7	6.5	5.2–8.2	
Hypercalcaemia						0.0005
No	564	77	22	15.3	13.8–17.8	
Yes	164	23	10	9.2	7.1–14.0	
Nephrectomy performed						<0.0001
Yes	457	61	25	18.3	15.8–20.9	
No	287	39	10	9.1	7.5–11.5	
Clearcell histology						<0.0001
Yes	612	83	21	15.3	14.0–17.7	
No	136	17	12	6.7	5.2–11.1	
Less than 1 year from diagnose						<0.0001
Yes	555	75	15	11.5	10.0–13.5	
No	189	25	30	26.8	23.2–31.1	
CNS metastases						0.0064
Yes	52	7	15	7.6	4.0–12.7	
No	692	93	19	14.7	13.4–16.2	
Liver metastases						<0.0001
Yes	157	21	13	8.1	6.5–10.6	
No	587	79	21	15.8	14.2–17.9	
Metastatic sites						<0.0001
1–2	369	50	25	17.9	15.4–20.8	
More than 2	375	50	13	10.7	8.9–12.6	
Start year						
2006	113	15	10	11.5	9.1–14.8	
2007	141	19	11	14.3	10.8–18.2	0.284[a]

Table 3 (*continued*)

Risk factor	*N*	%	% Alive	Median OS	95% CI	*P* value
2008	162	22	18	13.4	10.7–17.9	0.208[a]
2009	165	22	20	14.7	12.4–18.2	0.205[a]
2010	163	22	33	17.2	13.5–23.1	0.0435[a]

mRCC, metastatic Renal Cell Carcinoma; *N*, number; OS, overall survival; CI, confidence interval; PS, performance status; LLN, lower level of normal; LDH, lactate dehydrogenase; ULN, Upper Level of Normal.

[a] Compared to 2006.

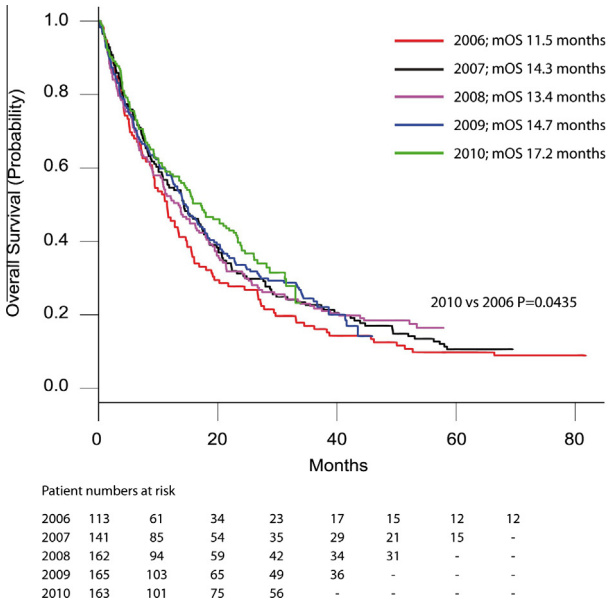

Fig. 1. Kaplan–Meier estimates of overall survival in Danish mRCC patients receiving treatment.

patients in PS 2–3 (HR 0.64, 95% CI, 0.51–0.80; $P < 0.0001$). Treatment start year 2008, 2009 and 2010 compared to 2006 were all independently associated with longer OS.

4. Discussion

This study is to our knowledge the first complete national assessment of the implementation of targeted therapy for patients with mRCC. We observed a significant increase in the number of patients referred for treatment; a significant increase in patients receiving treatment; a significant increase in additional treatment lines received; a change from immunotherapy to targeted therapy and an increased OS for patients receiving treatment whereas survival rate for untreated patients remained unchanged. These data emphasise a new era for patients with mRCC.

Large randomised trials have shown an improved PFS for patients treated with targeted agents, but only temsirolimus has demonstrated a significant OS benefit [1–5]. Lack of improved OS in clinical trials could be explained by confounding due to cross-over or treatment effects from subsequent treatment lines. Retrospective studies [11,12] and expanded access programmes [9,13,14] have indicated that there is a survival benefit for 'real-world' patients, however, these studies contained a mix of first, second and third line patients. Large epidemiological registry-based studies [15,16] have shown an improved OS, but these results were based on either a mix of patients with RCC and mRCC or lack of information regarding the fraction of treated patients. Poprach et al. [17] reported results from the Czech Republic national mRCC database, but this study omitted patients receiving immunotherapy and was therefore not a complete national cohort. Our study is the first report to document an improved OS in a complete national cohort of treated patients with confirmed mRCC.

Our study is also the first to provide detailed information regarding sequential therapies and histological subtype in a complete national cohort. The proportion of patients receiving first line and subsequent treatment lines increased significantly during the study period. Part of the increase in referred patients could be caused by the general increase in incidence rate of renal cell carcinoma. Approximately only one third of the patients received an additional treatment line after failure of the previous one. This proportion, however, increased significantly from 20% in 2006 to 40% in 2010 for second line treatment; similar to Heng et al. [18] where approximately 40% of anti-VEGF-treated patients received further treatment. Unfortunately, there is still a high proportion of real-life patients that are not able to receive further treatment despite the availability of several new treatment options.

During implementation of new treatment strategies it is expected that there will be a lag period before an impact on OS is seen. We observed a tendency towards improved year-by-year OS from 11.5 months in 2006 where the first Danish patients received targeted therapy to 17.2 months in 2010 where the majority received targeted therapy and we suggest that this improvement was caused by the new treatment opportunities. Other factors may have affected the outcome, e.g. improved supportive care, although one would then have expected to find a similar increase in OS for untreated patients. The significant prognostic factors from the multivariate analysis were in accordance with previous findings [10,11]. Moreover; the improved survival rate is not explained by a changed distribution in validated [19] prognostic factors according to Heng as these were evenly distributed between patients starting treatment in 2006 and 2010. Significantly fewer patients

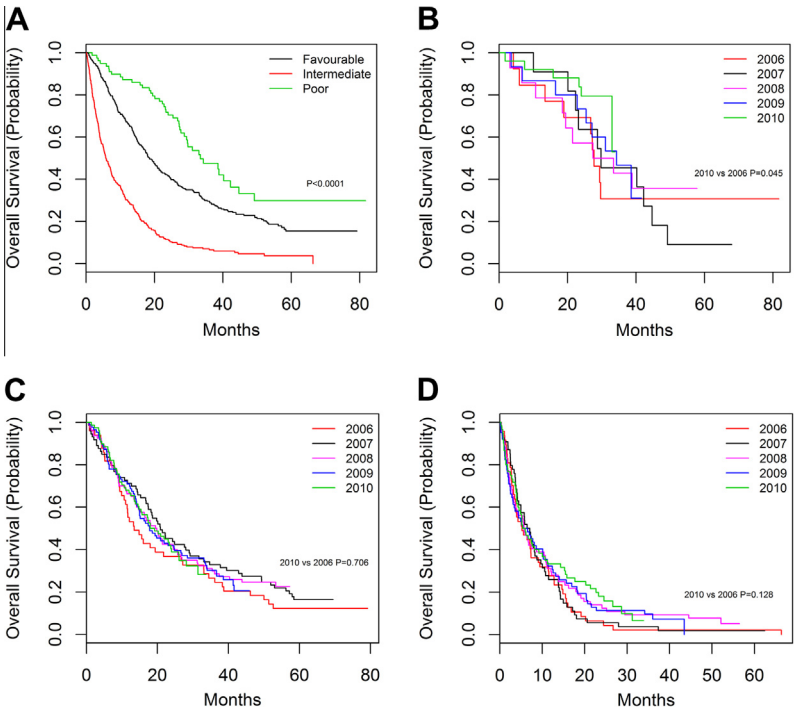

Fig. 2. Kaplan–Meier estimates of overall survival (OS) over time for Hengs prognostic groups for Danish patients treated for mRCC. (A) Overall survival for Hengs favourable, intermediate and poor risk group were 33.4, 18.6 and 5.8 months, respectively. (B) Overall survival for Hengs good prognosis group over time; 2006 median OS 27.8 months (95% CI, 18.9-NA) versus 2010 median OS not reached (95% CI, 33.0-NA). (C) Overall survival for Hengs intermediate prognosis group over time; 2006 median OS 13.4 months (95% CI, 11.0–27.1) versus 2010 median OS 18.6 months (95% CI, 14.8–26.0). (D) Overall survival for Hengs poor prognosis group over time; 2006 median OS 5.2 months (95% CI, 3.7–9.4) versus 2010 median OS 5.7 months (95% CI, 4.3–10.7).

Table 4
Multivariate analysis of predictors of overall survival for Danish patients treated for mRCC between 2006 and 2010. $N = 688$[a]

Risk factor	Hazard ratio	95% CI	*P* value
PS 0–1 and 3–6 versus 1–2 treatment lines	0.76	0.58–0.99	0.0397
PS 2–3 and 3–6 versus 1–2 treatment lines	0.19	0.06–0.60	0.0051
1–2 treatment lines and PS 0–1 versus PS 2–3	0.64	0.51–0.80	<0.0001
Haemoglobin below LLN	1.83	1.51–2.23	<0.0001
LDH above 1.5× ULN	2.75	2.06–3.67	<0.0001
Platelets above ULN	1.24	1.01–1.53	0.0404
Neutrophils above ULN	1.64	1.35–1.99	<0.0001
Hypercalcaemia	1.22	0.99–1.50	0.0594
No nephrectomy performed	1.17	0.97–1.42	0.1091
Clearcell histology	0.63	0.50–0.79	<0.0001
Less than 1 year from diagnose	1.36	1.07–1.72	0.0106
CNS metastases	1.33	0.94–1.87	0.1028
Liver metastases	1.11	0.90–1.38	0.3248
More than 2 metastatic sites	1.25	1.05–1.50	0.0132
Startyear 2007 versus 2006	0.86	0.64–1.14	0.2897
Startyear 2008 versus 2006	0.74	0.55–0.99	0.0415
Startyear 2009 versus 2006	0.72	0.54–0.96	0.0277
Startyear 2010 versus 2006	0.63	0.47–0.86	0.0035

mRCC, metastatic renal cell carcinoma; *N*, number; CI, confidence interval; PS, performance status; LLN, lower level of normal; LDH, lactate dehydrogenase; ULN, Upper Level of Normal.

[a] 56 patients deleted due to missing values. The model was corrected for interaction between performance status and numbers of treatment lines received.

had CNS metastases in 2006 compared to 2010 possibly reflecting that these patients were not referred to our departments due to the relative contraindication for immunotherapy. The difference in the distribution of hypercalcaemia likely reflects lead time bias as more patients were treated before hypercalcaemia developed

due to knowledge of better treatment options in 2010 compared to 2006. The apparently low nephrectomy rate may reflect reluctance to perform major surgery in patients with many risk factors in the absence of randomised trials supporting debulking nephrectomy in the era of targeted therapy. A similar nephrectomy-rate has been published from Sweden [16]. The multivariate analysis demonstrated that patients who received more than two treatment lines had a longer OS both for patients in good and poor PS. Treatment year 2008, 2009 and 2010 compared to 2006 were independently associated with longer OS which may be explained by better patient selection to relevant treatment or by other unknown confounding factors. It should be noted that 39% were in Hengs poor risk group and 16% had non-clearcell histology which has recently been associated with an inferior outcome [20]. Nevertheless, we were able to demonstrate a survival benefit from therapy in the complete cohort of patients.

Our results suggest that the improved OS over the years reflects the availability of more treatment options over time for use in sequential treatment as shown by the multivariate analysis that demonstrates a significant improved OS for patients receiving more than two treatment lines. We therefore suggest that the OS benefit observed in this heterogeneous cohort of patients is the result of the total amount of consecutive treatments, and not restricted to the individual treatments *per se*.

In 2009, the Danish health authorities implemented structural changes to speed up the diagnostic process and established a fast track for the treatment of cancer nationally. The present study does not allow for assessment of such changes as the impact of these initiatives will have a lag period. Nevertheless, the high proportion of referred but untreated patients and their dismal median OS of only 3.0 months from the date of metastatic disease highly emphasise the need for initiatives to reduce time for diagnostic work-out and referrals.

There are limitations to our study due to the retrospective design. Importantly the survival data are complete due to the unique Danish social security number system.

5. Conclusion

This is the first retrospective study to document that the implementation of targeted therapy has resulted in improved treatment rates and overall survival in a complete national cohort of treated patients with confirmed mRCC.

6. Conflict of interest statement

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Role of the funding source

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.10.010.

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