available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Synchronous Versus Metachronous Metastatic Disease: Impact of Time to Metastasis on Patient Outcome—Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Frede Donskov [a,*], *Wanling Xie* [b], *Anders Overby* [a], *J. Connor Wells* [c], *Anna P. Fraccon* [d], *Cosimo S. Sacco* [d], *Camillo Porta* [e], *Igor Stukalin* [c], *Jae-Lyun Lee* [f], *Konstantinos Koutsoukos* [g], *Takeshi Yuasa* [h], *Ian D. Davis* [i], *Carmel Pezaro* [i], *Ravindran Kanesvaran* [j], *Georg A. Bjarnason* [k], *Hao-Wen Sim* [l], *Nityam Rathi* [m], *Christian K. Kollmannsberger* [n], *Christina M. Canil* [o], *Toni K. Choueiri* [b], *Daniel Y.C. Heng* [c]

[a] *Aarhus University Hospital, Aarhus, Denmark;* [b] *Dana-Farber Cancer Institute, Boston, MA, USA;* [c] *Tom Baker Cancer Center, Calgary, Canada;* [d] *Medical Oncology Unit, Ospedale Pederzoli, Peschiera del Garda, Verona, Italy;* [e] *IRCCS San Matteo University Hospital, Pavia, Italy;* [f] *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;* [g] *Nation and Kapodistrian University of Athens, Athens, Greece;* [h] *Cancer Institute Hospital, Tokyo, Japan;* [i] *Monash University and Eastern Health, Melbourne, Australia;* [j] *National Cancer Centre Singapore, Singapore;* [k] *Sonnybrook Odette Cancer Center, Toronto, Canada;* [l] *Princess Margaret Cancer Centre, Toronto, Canada;* [m] *Huntsman Cancer Institute, Salt Lake City, UT, USA;* [n] *British Columbia Cancer Agency, Vancouver, Canada;* [o] *Ottawa Hospital Cancer Centre, Ottawa, Canada*

Article info

Article history:
Received 1 November 2019
Received in revised form
23 December 2019
Accepted January 14, 2020

Associate Editor:
Gianluca Giannarini

Keywords:
Advanced kidney cancer
International Metastatic Renal Cell Carcinoma Database Consortium

Abstract

Background: Patients with metastatic renal cell carcinoma (mRCC) may present with primary metastases (synchronous disease) or develop metastases during follow-up (metachronous disease). The impact of time to metastasis on patient outcome is poorly characterised.

Objective: To characterise overall survival (OS) and time to treatment failure (TTF) based on time to metastasis in mRCC patients treated with targeted therapy (tyrosine kinase inhibitors [TKIs]).

Design, setting, and participants: We used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) to compare synchronous (metastases within ≤3 mo of initial diagnosis of cancer) versus metachronous disease (evaluated by >3–12 mo, >1–2 yr, >2–7 yr, and >7 yr intervals).

Outcome measurements and statistical analysis: OS and TFF were assessed using Kaplan-Meier curves. Cox multivariable regressions analyses (MVAs) were adjusted for baseline factors.

Results and limitations: Of 7386 patients with mRCC treated with first-line TKIs, 3906 (53%) and 3480 (47%) had synchronous and metachronous metastasis, respectively. More patients with synchronous versus metachronous disease had

* Corresponding author. Department of Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. Tel. +45 4046 5234.
E-mail address: fd@oncology.au.dk (F. Donskov).

https://doi.org/10.1016/j.euo.2020.01.001

Retrospective
Synchronous
Metachronous
Renal cell carcinoma
Metastatic renal cell carcinoma

higher T stage (T1–2: 19% vs 34%), N1 disease (21% vs 6%), presence of sarcomatoid differentiation (15.8% vs 7.9%), Karnofsky performance status <80 (25.9% vs 15.1%), anaemia (62.5% vs 42.3%), elevated neutrophils (18.9% vs 10.9%), elevated platelets (21.6% vs 11.4%), bone metastases (40.4% vs 29.8%), and IMDC poor risk (40.6% vs 11.3%). Synchronous versus metachronous disease by intervals >3–12 mo, >1–2 yr, >2–7 yr, and >7 yr correlated with poor TTF (5.6 mo vs 7.3, 8.0, 10.8, and 13.3 mo, $p < 0.0001$) and poor OS (median 16.7 mo vs 23.8, 30.2, 34.8, and 41.7 mo, $p < 0.0001$). In MVAs, the adjusted hazard ratios (95% confidence intervals) were 1.00 (reference), 0.98 (0.90–1.06), 0.81 (0.73–0.91), 0.74 (0.68–0.81), and 0.60 (0.54–0.67), respectively, for OS ($p < 0.0001$), and 1.00 (reference), 0.99 (0.92–1.06), 0.98 (0.90–1.07), 0.83 (0.77–0.89), and 0.66 (0.60–0.72), respectively, for TTF ($p < 0.0001$). Data were collected retrospectively.

Conclusions: Timing of metastases after initial RCC diagnosis may impact the outcomes from targeted therapy in mRCC.

Patient summary: We looked at the impact of the timing of metastatic outbreak on survival outcomes in kidney cancer patients treated with targeted therapy. We found that the longer time to metastatic development was associated with improved outcome.

1. Introduction

Worldwide, a total of 400 000 new cases of and 175 000 deaths from renal cell cancer were estimated in 2018, making this cancer the 13th most commonly diagnosed solid malignancy [1]. Approximately 15% of patients present with synchronous metastatic disease at the time of diagnosis, that is, patients are diagnosed with a primary kidney tumour and metastases simultaneously [2], and approximately 20% of patients with nonmetastatic disease at initial nephrectomy develop metachronous metastatic disease, that is, develop metastases during follow-up [3]. In metastatic renal cell carcinoma (mRCC), surgery is often not applicable due to widespread metastatic disease [4]; thus, systemic therapy is applicable in this setting [5,6].

The impact of time from initial RCC diagnosis to the initiation of oncologic therapy of <12 mo was established as an independent poor prognostic marker included in the Memorial Sloan Kettering Cancer Center (MSKCC) model [7], developed in the era of interferon. In the era of targeted tyrosine kinase inhibitors (TKIs), the time interval of <1 yr from the primary diagnosis to the start of oncologic treatment was encompassed in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model together with Karnofsky performance status of <80%, hypercalcaemia, anaemia, neutrophilia, and thrombocytosis. According to the number of poor prognostic factors, patients were divided in both MSKCC and IMDC models into prognostic groups: favourable (zero risk factors), intermediate (one to two risk factors), and poor (three or more risk factors) [8]. The IMDC model has subsequently been validated in clear cell RCC [8] and non–clear cell RCC, including papillary RCC [9,10]. The <12 mo cut-off is arbitrary, and more detailed prognostic information regarding the time to metastasis (TTM) outbreak is needed.

Patients with mRCC form a heterogeneous group with varying outcomes ranging from weeks to several years. Synchronous disease may represent a distinct pathologic and molecular phenotype [11]. The impact of timing of metastatic disease recurrence on outcomes from TKIs is poorly characterised. We, therefore, assessed the IMDC database to evaluate the impact of synchronous versus metachronous mRCC outbreak for patient outcome on targeted therapy.

2. Patients and methods

2.1. Patient population

The IMDC database is a consecutive patient series comprising international academic centres in Canada, USA, Denmark, Italy, Greece, Japan, South Korea, Singapore, and Australia. We used the database to investigate the impact of metastatic timing on survival outcomes in RCC. We retrospectively collected baseline demographic, clinical, and pathologic report, and laboratory data using uniform database templates to ensure consistent data collection [12]. Survival data were collected from patients' medical records. Data were collected from 2003 until 2016. Patient inclusion criteria comprised a diagnosis of mRCC of any histologic subtype treated with first-line targeted therapy. Patients were excluded from the analysis if they had missing information regarding the date of metastasis and date of diagnosis, or excluded due to no survival follow-up data. This study received ethics committee or institutional review board approval as applicable from each participating centre.

2.2. Statistical analysis

Analyses compared synchronous disease, defined as metastases within ≤3 mo of initial diagnosis of RCC, versus metachronous disease, defined as metastasis diagnosed after initial diagnosis. TTM was initially analysed as a continuous variable (with 1 yr increments). As results suggested that the association of TTM with OS and time to treatment failure (TTF) did not follow a linear relationship, we therefore regrouped patients into the following intervals: ≤3 mo, >3–12 mo, >1–2 yr, >2–7 yr, and >7 yr, according to the observed clinical pattern. The date of initial diagnosis was defined as the date of histologic confirmation of RCC—the date of either nephrectomy or biopsy. Overall survival (OS) was defined from the initiation of first-line target therapy to the date of death or being censored at the last follow-up. TTF was defined as the time from the initiation of targeted therapy to treatment discontinuation for any reason, including death, disease progression (according to RECIST v1.1 [13]), treatment toxicity, or being censored at the last follow-up. The best objective response rate was defined using investigator-assessed complete response and partial response according to RECIST 1.1.

Distributions of OS and TTF were estimated using the Kaplan-Meier methodology. Median and 95% confidence intervals (CIs) were provided. Cox multivariable regression analyses assessed the hazard ratios (HRs) of metachronous versus synchronous mRCC, adjusting for baseline factors including IMDC risk features; T and N stages at cancer diagnosis; histology (clear cell vs non–clear cell); presence of sarcomatoid differentiation (yes or no); number of metastasis; presence of bone, liver, or brain metastasis (yes or no); age at TKI initiation; and era of TKI initiation (2003–2007, 2008–2012, and 2013–2016).

Statistical analyses were performed using the SAS software application (version 9.4; SAS Institute, Cary, NC, USA). Two-sided p values were reported.

3. Results

3.1. Patient characteristics

At the time of analysis, the database covered the data of 7498 patients, of whom 7386 were included for this analysis; 112 were excluded due to missing data on the date of metastasis or date of diagnosis (n = 80), or excluded due to no survival follow-up data (n = 32). Median follow-up from TKI initiation in alive patients was 26.5 mo (range: 0.1–130). A total of 2319 patients were alive at data cut-off.

The patient characteristics are summarised in Table 1. At initial cancer diagnosis, more patients with synchronous versus metachronous disease had higher T stage (T1–2: 19% vs 34%; T3–4: 45.4% vs 38.6%), N1 disease (21% vs 6%), and presence of sarcomatoid differentiation (15.8% vs 7.9%). At TKI initiation, more patients with synchronous versus metachronous disease had poor Karnofsky performance status <80 (25.9% vs 15.1%), low haemoglobin (62.5% vs 42.3%), elevated neutrophils (18.9% vs 10.9%), elevated platelets (21.6% vs 11.4%), and bone metastases (40.4% vs

Table 1 – Patient and disease characteristics.

	All (*N* = 7386)		Metachronous disease (*N* = 3480)		Synchronous disease (*N* = 3906)	
	N	%	*N*	%	*N*	%
At cancer diagnosis						
Age at diagnosis, median, IQR	59	52–67	58	50–65	61	53–68
Gender						
Female	1997	27	950	27.3	1047	26.8
Male	5388	72.9	2529	72.7	2859	73.2
T stage at diagnosis						
T1	917	12.4	596	17.1	321	8.2
T2	1024	13.9	604	17.4	420	10.8
T3–4	3120	42.2	1345	38.6	1775	45.4
Tx/unknown	2325	31.5	935	26.9	1390	35.6
N stage at diagnosis						
N0	2573	34.8	1472	42.3	1101	28.2
N1	1036	14.0	217	6.2	819	21.0
Nx/unknown	3777	51.1	1791	51.5	1986	50.8
Non–clear cell pathology						
No	6130	88.0	3016	90.0	3114	86.2
Yes	833	12.0	334	10.0	499	13.8
Unknown	423		130		293	
Presence of sarcomatoid differentiation						
No	5508	88.0	2740	92.1	2768	84.2
Yes	754	12.0	234	7.9	520	15.8
Unknown	1124		506		618	
Nephrectomy status						
No nephrectomy	1454	19.8	56	1.6	1398	36.1
Nephrectomy	3317	45.1	3317	95.4	0	0
Cytoreductive nephrectomy	2579	35.1	103	3.0	2476	63.9
Unknown	36		4		32	

Table 1 (*Continued*)

	All (*N* = 7386)		Metachronous disease (*N* = 3480)		Synchronous disease (*N* = 3906)	
	N	%	*N*	%	*N*	%
At TKI initiation						
Age at TKI start, median, IQR	62	55–69	63	56–71	61	54–68
Year of TKI initiation						
2003–2007	2148	29.1	1099	31.6	1049	26.9
2008–2012	3739	50.6	1720	49.4	2019	51.7
2013–2016	1499	20.3	661	19.0	838	21.5
KPS (<80)						
No	5306	79.2	2682	84.9	2624	74.1
Yes	1393	20.8	477	15.1	916	25.9
Unknown	687		321		366	
Hb < LLN						
No	3235	46.9	1857	57.7	1378	37.5
Yes	3661	53.1	1362	42.3	2299	62.5
Unknown	490		261		229	
Corrected Ca > ULN						
No	5405	86.2	2602	89.5	2803	83.3
Yes	867	13.8	306	10.5	561	16.7
Unknown	1114		572		542	
Neutrophil > ULN						
No	5674	84.8	2780	89.1	2894	81.1
Yes	1015	15.2	342	10.9	673	18.9
Unknown	697		358		339	
Platelets > ULN						
No	5611	83.2	2791	88.6	2820	78.4
Yes	1137	16.9	361	11.4	776	21.6
Unknown	638		328		310	
IMDC risk group						
Favourable	1118	17.9	930	32.5	188	5.5
Intermediate	3435	54.9	1607	56.2	1828	54.9
Poor	1698	27.2	323	11.3	1375	40.6
Unknown	1135		620		515	
Number of metastases						
1	1644	23.1	844	25.3	800	21.2
>1	5473	76.9	2493	74.7	2980	78.8
Unknown	269		143		126	
Brain metastasis						
No	6106	91.7	2883	92.4	3223	91.1
Yes	552	8.3	238	7.6	314	8.9
Unknown	728		359		369	
Bone metastasis						
No	4368	64.6	2219	70.2	2149	59.6
Yes	2398	35.4	941	29.8	1457	40.4
Unknown	620		320		300	
Live metastasis						
No	5183	78.9	2422	79.0	2761	78.9
Yes	1383	21.1	645	21.0	738	21.1
Unknown	820		413		407	
Type of first-line therapy						
Sunitinib	4962	67.2	2337	67.2	2625	67.2
Sorafenib	1004	13.6	513	14.7	491	12.6
Pazopanib	708	9.6	339	9.7	369	9.4
Temsirolimus	262	3.5	76	2.2	186	4.8
Bevacizumab	156	2.1	80	2.3	76	1.9
Everolimus	127	1.7	63	1.8	64	1.6
Other	84	1.1	34	1	50	1.3
Axitinib	48	0.6	28	0.8	20	0.5
AZD	35	0.5	10	0.3	25	0.6

Hb = haemoglobin; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IQR = interquartile range; KPS = Karnofsky performance status; LLN = lower limit of normal; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

29.8%), and were of IMDC poor-risk category (40.6% vs 11.3%). All patients received targeted therapy; most received first-line sunitinib followed by sorafenib and pazopanib (67.2%, 13.6%, and 9.6%, respectively).

A total of 3906 patients (53%) had synchronous metastatic disease and 3480 (47%) had metachronous disease. Association of TTM with patient characteristics is summarised in Table 2. Synchronous versus metachronous

Table 2 – Association of time to metastasis (TTM; five groups) with patient characteristics.

TTM	Age at diagnosis			Age at TKI initiation		Non–clear cell pathology		Number of IMDC risk factors		
	Evaluable *N*	Mean	STD	Mean	STD	Evaluable *N*	%	Evaluable *N*	Mean	STD
0–3 mo	3899	60	11	61	11	3613	14	3808	2.3	1.3
>3–12 mo	1054	59	11	61	11	1030	12	1023	1.6	1.2
>12–24 mo	637	59	11	62	11	628	10	614	0.9	1.0
>2–7 yr	1154	58	10	63	10	1108	10	1117	0.9	0.9
>7 yr	632	53	10	66	9	584	7	613	0.8	0.9
p value		<0.0001		<0.0001			<0.0001		<0.0001	

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; STD = standard deviation; TKI = tyrosine kinase inhibitor.

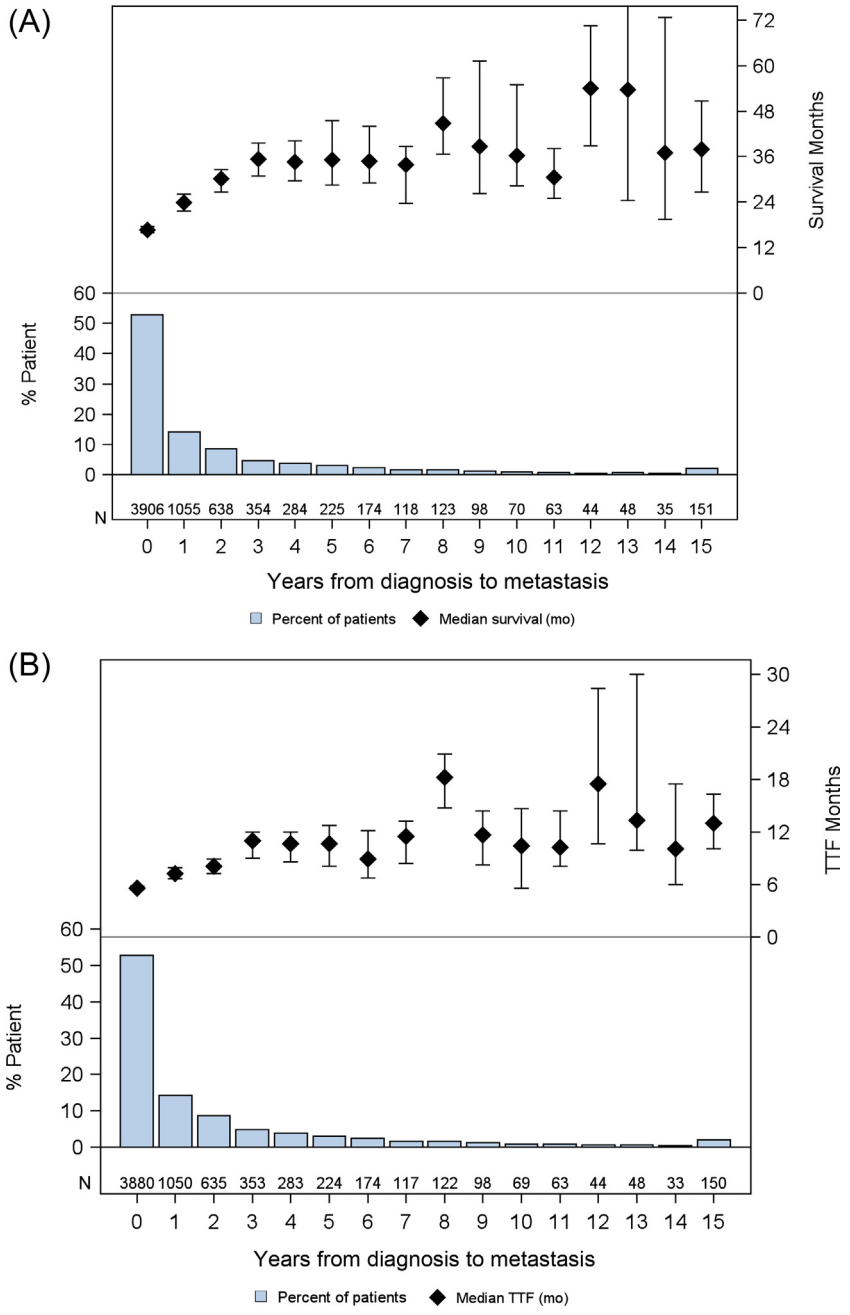

Fig. 1 – Percentage of patients who developed metastatic disease over time versus (A) median overall survival and (B) median time to treatment failure (TTF; 95% CI) from TKI initiation by year from diagnosis to metastasis.
CI = confidence interval; TKI = tyrosine kinase inhibitor.

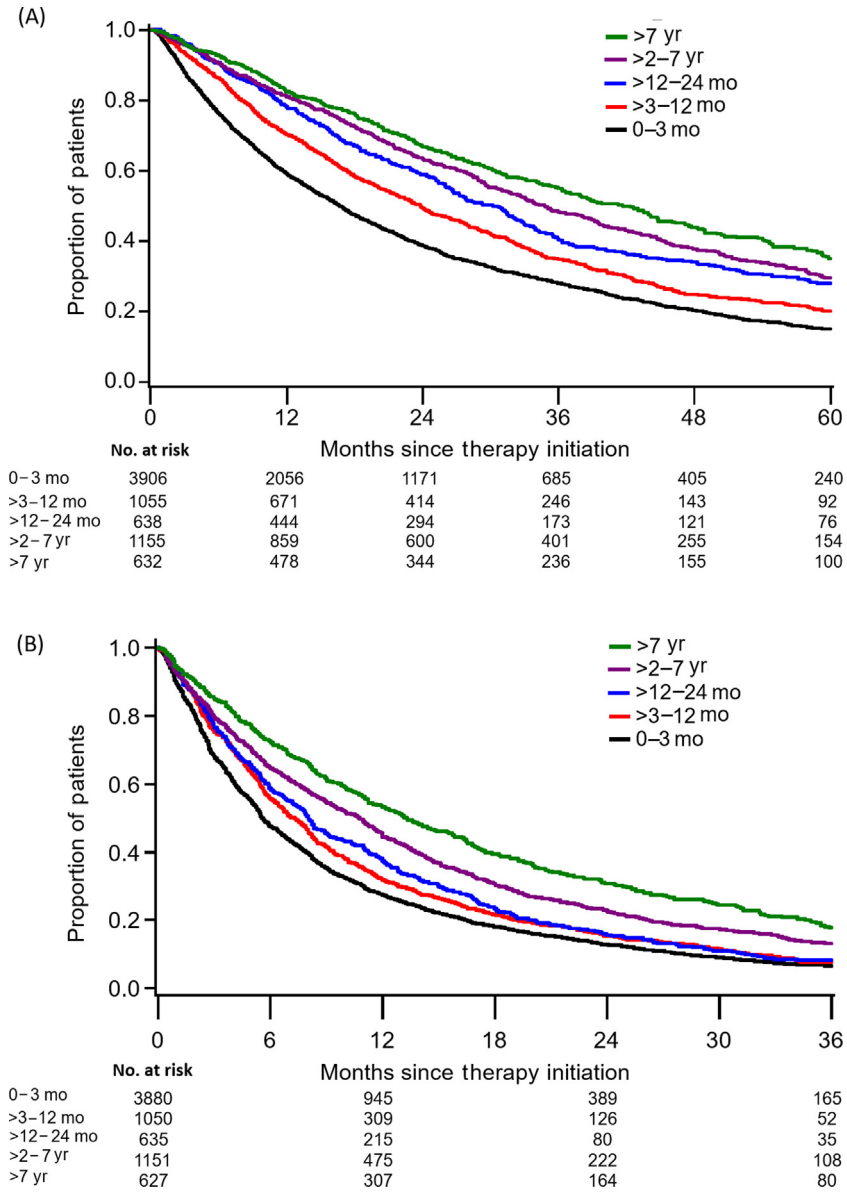

Fig. 2 – Kaplan-Meier graphs of (A) overall survival and (B) time to treatment failure (TTF) since TKI initiation by time from diagnosis to metastasis (five groups).
TKI = tyrosine kinase inhibitor.

disease by intervals >3–12 mo, >1–2 yr, >2–7 yr, and >7 yr correlated with higher age at initial diagnosis (mean 60 yr vs 59, 59, 58, and 53 yr; $p < 0.0001$), lower age at TKI initiation (mean 61 yr vs 61, 62, 63, and 66 yr; $p < 0.0001$), higher rate of non–clear cell histology (14% vs 12%, 10%, 10%, and 7%; $p < 0.0001$), and higher rate of IMDC risk features (mean 2.3 vs 1.6, 0.9, 0.9, and 0.8; $p < 0.0001$).

3.2. *Impact of TTM on outcome*

Patients with shorter TTM had worse OS and TTF from TKI initiation (Fig. 1). TTM was initially analysed as a continuous variable (with 1 yr increments). Results suggested that the association of TTM with OS and TTF did not follow a linear relationship. Shorter TTM was associated with increasing risk of death within 3 yr, but survival plateaued in patients with TTM 3–7 yr and in those with TTM > 7 yr. Therefore, we regrouped patients into intervals. Patients with synchronous disease had median OS of 16.7 mo (95% CI: 15.9–17.5). Patients with metachronous disease by intervals 3–12 mo, 12–24 mo, 2–7 yr, and >7 yr had OS of 23.8 mo (95% CI: 21.6–26.1), 30.2 mo (95% CI: 26.7–32.5), 34.8 mo (95% CI: 32.4–38.1), and 41.7 mo (95% CI: 36.3–46.0), respectively ($p < 0.0001$). Patients with synchronous disease had TTF of 5.6 mo (95% CI: 5.5–5.8). Patients with metachronous disease by interval 3–12 mo, 12–24 mo, 2–7 yr, and >7 yr intervals had TTF of 7.3 mo (95% CI: 6.6–8.0), 8.0 mo (95% CI: 7.3–8.9), 10.8 mo

Table 3 – Association of time-to-metastasis intervals (five groups) with overall survival (OS), time to treatment failure TTF, and objective response rate (ORR) from TKI initiation.

TTM	OS				TTF				ORR (CR + PR)			
	Total/failed	Median (mo) 95% CI	Adjusted[a] hazard ratio (95% CI)	Adjusted *p* value	Total/failed	Median (mo) 95% CI	Adjusted[a] hazard ratio (95% CI)	Adjusted *p* value	*N*	*N*/% (CR or PR)	Adjusted odds ratio	Adjusted *p* value
0–3 mo	3906/2852	16.7 (15.9–17.5)	1.00 (reference)	–	3880/3483	5.6 (5.5–5.8)	1.00 (reference)	–	3234	779(24%)	1.00 (reference)	–
>3–12 mo	1055/726	23.8 (21.6–26.1)	0.98 (0.90–1.06)	0.571	1050/941	7.3 (6.6–8.0)	0.99 (0.92–1.06)	0.738	902	248(27%)	0.98 (0.82–1.17)	0.823
>12–24 mo	638/401	30.2 (26.7–32.5)	**0.81 (0.73–0.91)**	0.0002	635/564	8.0 (7.3–8.9)	0.98 (0.90–1.07)	0.670	540	158(29%)	0.97 (0.78–1.20)	0.751
>2–7 yr	1155/729	34.8 (32.4–38.1)	**0.74 (0.68–0.81)**	<0.0001	1151/1011	10.8 (9.6–11.5)	**0.83 (0.77–0.89)**	<0.0001	971	318(33%)	**1.18 (1.00–1.40)**	0.054
>7 yr	632/359	41.7 (36.3–46.0)	**0.60 (0.54–0.67)**	<0.0001	627/527	13.3 (11.5–14.9)	**0.66 (0.60–0.72)**	<0.0001	554	212(38%)	**1.54 (1.25–1.89)**	<.0001
Total	7386/5067				7343/6526				6201			

CI = confidence interval; CR = complete response; Hgb = haemoglobin; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; PR = partial response; TKI = tyrosine kinase inhibitor; TTM = time to metastasis.

[a] From multivariable Cox regression, adjusted for T and N stages at cancer diagnosis; histology (clear cell vs non–clear cell); presence of sarcomatoid differentiation (yes or no); IMDC risk factor (Hgb, corrected calcium, neutrophil, platelets, KPS); number of metastasis (1 vs >1); presence of bone, liver, or brain metastasis (yes or no); age at TKI initiation; and year of TKI initiation (2003–2007, 2008–2012, and 2013–2016). An unknown category was included if missing values were present for a covariate).

(95% CI: 9.6–11.5), and 13.3 mo (95% CI: 11.5–14.9), respectively ($p < 0.0001$). Fig. 2 displays Kaplan-Meier curves of OS (Fig. 2A) and TTF (Fig. 2B) assessed by time intervals.

In the multivariable Cox regression analysis compared with synchronous disease, TTM interval of >1 yr was independently associated with improved OS, after adjusting for confounding factors (TTM of 12–24 mo, HR: 0.81, $p = 0.002$; TTM of 2–7 yr, HR: 0.74, $p < 0.001$; and TTM of >7 yr, HR: 0.60, $p < 0.001$). Improved TTF was seen for TTM interval of >2 yr (TTM of 2–7 yr, HR: 0.83, $p < 0.001$; and TTM of >7 yr, HR: 0.66, $p < 0.001$). In addition, improved adjusted odds ratio (OR) was seen for TTM intervals of >2 yr (TTM of 2–7 yr, OR: 1.18, $p < 0.054$; and TTM of >7 yr, OR: 1.54, $p < 0.001$; Table 3).

4. Discussion

To date, this study is the largest analysis demonstrating that the timing of metastases after initial RCC diagnosis impacts outcome from target therapy in mRCC. Patients with synchronous disease compared with patients with metachronous disease have more adverse prognostic features, significantly shorter TTF, and poorer survival. This may help in patient counselling and may be taken into consideration in clinical trial designs in the future, in order to avoid an imbalance between treatment arms.

A compilation of 11 pivotal first-line trials in mRCC is presented in Table 4, indicating which clinical trials took into account the time to development of metastases [14–24]. Two studies had information of time <1 yr from the initial diagnosis to systemic treatment available for each arm, and one study had this information available for the whole cohort only. One study had information of median time since the initial diagnosis. The remaining seven studies had MSKCC and/or IMDC risk group information as the only baseline information of the metastatic timing, with no elaboration of the distribution of the five and six poor-risk features, respectively. No study was stratified for the time to development of metastases. However, six studies were stratified for IMDC or MSKCC prognostic risk factors. Patients with favourable prognostic features have >1 yr from the initial diagnosis to oncologic treatment by definition, but full information on metastatic timing was not interpretable. Therefore, the poor outcome of synchronous mRCC may have been masked in the pivotal studies as TTM was not accounted for. The median OS of 16.7 mo for patients with synchronous mRCC observed in this study is in line with the OS observed in two prospective studies conducted in patients with synchronous mRCC: SURTIME (15.0 mo for immediate cytoreductive nephrectomy followed by sunitinib) [25] and CARMENA (18.4 and 13.9 mo) [26]. Moreover, the current study provides further details and emphasises the impact of metastatic timing.

The findings in this study are consistent with previous evidence that early metastasis is associated with an adverse effect on outcome and response to targeted treatment [11]. Synchronous mRCC compared with metachronous disease is associated with poorer Eastern Cooperative

Table 4 – Information on time from initial diagnosis to metastasis in pivotal metastatic RCC trials.

Trials	Year	Experimental	Control	Information of <1 yr from initial diagnosis to treatment	Baseline information MSKCC/IMDC	Stratification including metastatic timing
Motzer et al [14]	2007	Sunitinib	Interferon-α	Yes (not per arm)	MSKCC	No
AVOREN [15]	2007	Bevacizumab + interferon-α	Interferon-α	Yes	MSKCC	MSKCC
Global ARCC [16]	2007	Temsirolimus	Interferon-α	Yes	MSKCC	No
CALGB 90206 [17]	2008	Bevacizumab + interferon-α	Interferon-α	No	MSKCC	MSKCC
Sternberg et al [18]	2010	Pazopanib	Placebo	No[a]	MSKCC	No
COMPARZ [19]	2013	Pazopanib	Sunitinib	No	MSKCC + IMDC	No
CABOSUN [20]	2016	Cabozantinib	Sunitinib	No	IMDC	IMDC
CheckMate-214 [21]	2018	Nivolumab + ipilimumab	Sunitinib	No	IMDC	IMDC
Immotion-151 [22]	2019	Bevacizumab + atezolizumab	Sunitinib	No	MSKCC	MSKCC
Javelin Renal 101 [23]	2019	Avelumab + axitinib	Sunitinib	No	MSKCC + IMDC	No
KEYNOTE-426 [24]	2019	Pembrolizumab + axitinib	Sunitinib	No	IMDC	IMDC

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma.
[a] Information of median time since initial diagnosis is provided.

Oncology Group (ECOG) performance status score and worse risk group in both MSKCC and IMDC, and corresponds to a more aggressive tumour with higher pT status, higher rate of sarcomatoid component, overexpression of vascular endothelial growth factor, PAR-3, and PD-L1 [11]. Recently, the evolutionary trajectories of kidney cancer were described in more detail by the TRACERx Renal study. Clear cell RCC is caused by consecutive genetic events: loss of chromosome 3p, followed by mutation or methylation in VHL are the basic genetic events, followed by mutations in PBRM1, SETD2, and BAP1 followed by the loss of chromosomes 9p and 14q [27,28]. The more the genetic events, the more aggressive the phenotypes, with patient prognosis associated with the subclonal composition of their disease [28]. Distinct evolutionary trajectories have been established in the metastatic setting; disease progression depends on the composition of mutational events, presenting as either punctuated evolution (early acquisition of multiple clonal drivers, with high chromosomal complexity and low intratumour heterogeneity), which leads to rapid dissemination and an aggressive disease, or branched evolution (plural subclonal drivers, with moderate chromosomal complexity and high intratumour heterogeneity) with an attenuated progression, characterised by an initial solitary metastatic pattern [29]. Another recent study showed a correlation between IMDC risk features and specific molecular profiles of clear cell RCC [30]. Taken together, the heterogeneous biology of RCC translates to diverse clinical outcomes; hence, the current risk models are a surrogate measure of the underlying tumour biology. The implication is that a high proportion of patients with synchronous disease have tumours with punctuated evolution, harbouring aggressive disease features, consolidating in worse risk factors, requiring systemic therapy earlier, and having almost half the expected survival after the initiation of targeted therapy compared with the latest metastatic timing, as shown in our study. Thus, the clinical impact of metastatic timing in our study reflects the underlying aggressive tumour biology. Whether TTM impacts outcome to checkpoint immunotherapy is yet to be elucidated.

The strength of this study lies in the large data set, including the large number of nontrial patients reflecting real-word patients. Limitations to our study included the retrospective design. Although the included patients are consecutive patients, there is a probability of bias. However, the use of consecutive patient series attempted to mitigate some of the deficiencies.

5. Conclusions

Timing of metastases after initial RCC diagnosis impacts outcome from targeted therapy in mRCC. This may need to be taken into consideration in clinical trial designs, and may help in patient counselling and prognostication.

Author contributions: Frede Donskov had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Donskov, Choueiri, Heng.
Acquisition of data: Donskov, Wells, Fraccon, Sacco, Porta, Stukalin, Lee, Koutsoukos, Yuasa, Davis, Pezaro, Kanesvaran, Bjarnason, Sim, Rathi, Kollmannsberger, Canil, Choueiri, Heng.
Analysis and interpretation of data: Donskov, Xie, Overby, Wells, Fraccon, Sacco, Porta, Stukalin, Lee, Koutsoukos, Yuasa, Davis, Pezaro, Kanesvaran, Bjarnason, Sim, Rathi, Kollmannsberger, Canil, Choueiri, Heng.
Drafting of the manuscript: Donskov, Xie, Overby, Wells, Fraccon, Sacco, Porta, Stukalin, Lee, Koutsoukos, Yuasa, Davis, Pezaro, Kanesvaran, Bjarnason, Sim, Rathi, Kollmannsberger, Canil, Choueiri, Heng.
Critical revision of the manuscript for important intellectual content: Donskov, Xie, Overby, Wells, Fraccon, Sacco, Porta, Stukalin, Lee, Koutsoukos, Yuasa, Davis, Pezaro, Kanesvaran, Bjarnason, Sim, Rathi, Kollmannsberger, Canil, Choueiri, Heng.
Statistical analysis: Xie.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other: None.

Financial disclosures: Frede Donskov certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the

manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Frede Donskov: reports grant to institution from Pfizer and Ipsen. Toni Choueiri: research (institutional and personal)—AstraZeneca, Alexion, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Lilly, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Analysis Group, Sanofi/Aventis, and Takeda; honoraria—AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Michael J. Hennessy (MJH) Associates, Inc. (healthcare communications company with several brands such as OnClive, PeerView, and PER), Research to Practice, L-path, *Kidney Cancer Journal*, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, *NEJM*, *Lancet Oncology*, Heron Therapeutics, and Lilly; consulting or advisory role—AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Heron Therapeutics, Lilly, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Pionyr, and Tempest; stock ownership—Pionyr and Tempest; no leadership or employment in for-profit companies; other present or past leadership roles—Director of GU Oncology Division at Dana-Farber and past President of medical Staff at Dana-Farber, member of NCCN Kidney Panel and the GU Steering Committee, and past Chairman of the Kidney Cancer Association Medical and Scientific Steering Committee; patents, royalties, or other intellectual properties—International Patent Application No. PCT/US2018/12209, entitled "PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response," filed January 3, 2018, claiming priority to U.S. Provisional Patent Application No. 62/445,094, filed January 11, 2017; and International Patent Application No. PCT/US2018/058430, entitled "Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy," filed October 31, 2018, claiming priority to U.S. Provisional Patent Application No. 62/581,175, filed November 3, 2017. Hao-Wen Sim: research funding (institutional)—Abbvie and Bristol-Myers Squibb. Ian Davis: supported by an NHMRC Practitioner Fellowship (APP1102604). Ravindran Kanesvaran: speaker bureau and received honoraria from Novartis, Ipsen, Pfizer, BMS, Merck, Eisai, Amgen, Astellas, and Janssen. Anders Overby: travel support for conference from Ipsen. Connor Wells: travel support from Pfizer. Daniel Heng: grants and personal fees from Pfizer, Novartis, BMS, and Ipsen; personal fees from Merck. Christina Canil: personal fees from Pfizer, Eisai, Merck, EMD Seromo, Novartis, Bayer, BMS, AstraZeneca, Ipsen, and Roche; travel grant to attend conference from Amgen, Sanofi, and Pfizer. No other authors declare any conflicts of interest.

***Funding/Support and role of the sponsor*:** This work was supported by the IMDC. Frede Donskov received a research grant from Health Research Foundation of Central Denmark region.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.

[3] Dabestani S, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. World J Urol 2016;34:1081–6.

[4] Larcher A, Wallis CJD, Bex A, et al. Individualised indications for cytoreductive nephrectomy: which criteria define the optimal candidates? Eur Urol Oncol 2019;2:365–78.

[5] Hahn AW, Klaassen Z, Agarwal N, et al. First-line treatment of metastatic renal cell carcinoma: a systematic review and network meta-analysis. Eur Urol Oncol 2019;2:708–15.

[6] de Velasco G, Bex A, Albiges L, et al. Sequencing and combination of systemic therapy in metastatic renal cell carcinoma. Eur Urol Oncol 2019;2:505–14.

[7] Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol 2002;20:2376–81.

[8] Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141–8.

[9] Kroeger N, Xie W, Lee JL, et al. Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: characterization of survival outcome and application of the International mRCC Database Consortium criteria. Cancer 2013;119:2999–3006.

[10] Connor Wells J, Donskov F, Fraccon AP, et al. Characterizing the outcomes of metastatic papillary renal cell carcinoma. Cancer Med 2017;6:902–9.

[11] Kammerer-Jacquet SF, Brunot A, Pladys A, et al. Synchronous metastatic clear-cell renal cell carcinoma: a distinct morphologic, immunohistochemical, and molecular phenotype. Clin Genitourin Cancer 2017;15:e1–7.

[12] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794–9.

[13] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[14] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.

[15] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103–11.

[16] Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–81.

[17] Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26:5422–8.

[18] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.

[19] Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722–31.

[20] Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. J Clin Oncol 2017;35:591–7.

[21] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.

[22] Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393:2404–15.

[23] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.

[24] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–1127.

[25] Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. JAMA Oncol 2019;5:164–70.

[26] Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379:417–27.

[27] Mitchell TJ, Turajlic S, Rowan A, et al. Timing the landmark events in the evolution of clear cell renal cell cancer: TRACERx Renal. Cell 2018;173:611–623.e617.

[28] Turajlic S, Xu H, Litchfield K, et al. Deterministic evolutionary trajectories influence primary tumor growth: TRACERx Renal. Cell 2018;173:595–610.e511.

[29] Turajlic S, Xu H, Litchfield K, et al. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. Cell 2018;173:581–594.e512.

[30] Verbiest A, Renders I, Caruso S, et al. Clear-cell renal cell carcinoma: molecular characterization of IMDC risk groups and sarcomatoid tumors. Clin Genitourin Cancer 2019;17:e981–94.