www.medscape.com

Targeted Therapies in Advanced Renal Cell Carcinoma

The Role of Metastatic Sites as a Prognostic Factor

Paolo Grassi, Elena Verzoni, Luca Porcu, Isabella Testa, Roberto Iacovelli, Valter Torri, Filippo de Braud, Giuseppe Procopio

Future Oncol. 2014;10(8):1361-1372.

Abstract and Introduction

Abstract

Aim: This retrospective study evaluates whether metastatic sites were associated with progression-free survival (PFS) and overall survival (OS) in patients with renal cell carcinoma treated with targeted therapies.

Patients & methods: In total, 358 patients were analyzed.

Results & conclusion: After a median follow-up of 56.1 months, median PFS was 11 months and median OS was 24.2 months. Metastatic sites were associated with PFS: lymph nodes (HR: 1.43; 95% CI: 1.12–1.83; p = 0.004), liver (HR: 1.41; 95% CI: 1.05–1.90; p = 0.021), bone (HR: 1.26; 95% CI: 0.96–1.65; p = 0.091), brain (HR: 0.81; 95% CI: 0.46–1.43; p = 0.474) and other sites (HR: 1.07; 95% CI: 0.83–1.38; p = 0.589). Metastatic sites were associated with OS: lymph nodes (HR: 1.73; 95% CI: 1.31–2.29; p < 0.001), liver (HR: 1.71; 95% CI: 1.23–2.37; p = 0.002), bone (HR: 1.48; 95% CI: 1.10–1.98; p = 0.009), brain (HR: 1.21; 95% CI: 0.64–2.28; p = 0.568) and other sites (HR: 1.09; 95% CI: 0.81–1.47; p = 0.568). Patients with >2 metastatic sites had shorter PFS and OS. Every association was lost when introducing the Motzer score in regression models.

Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all adult cancers and represents the third most common urologic malignancy in Europe[1]. At diagnosis, a third of the patients present with locally advanced or metastatic disease and a third of patients undergoing nephrectomy will eventually develop metastasis.[2,3] Frequent sites of metastasis include the lungs (50–60%), lymph nodes (60–65%), bone (30–40%), liver (20–40%) and the brain (5%).[4,5] Other rare metastatic sites include the pancreas, adrenal and parotid glands.[6,7]

The 5-year survival rate of untreated patients is less than 10%; however, the recent introduction in clinical practice of novel targeted agents for metastatic disease improved cancer-specific survival and changed the approach to metastatic RCC (mRCC). Validated prognostic factors, including time from diagnosis to treatment >12 months, levels of hemoglobin, lactate dehydrogenase and serum calcium levels, as well as the number of metastatic sites, have been identified from mRCC patients treated with cytokines. These factors are now used to categorize patients into good, intermediate and poor risk of recurrence.[8–11] In particular, the landmark study by Manola *et al.* analyzed a comprehensive international database of 3748 patients and identified nine independent predictors of survival including: treatment, performance status, number of metastatic sites, time from diagnosis to treatment, pretreatment hemoglobin, white blood count, alkaline phosphatase and serum calcium level.[11] These variables formed three risk groups using the 25th and 75th percentiles of the resulting prognostic index. However, it is not clear whether the pattern of metastatic spread or the specific site of metastatic disease could lead to any difference in terms of response to treatment or could predict differences in overall survival (OS), especially if we take into account that the available data used to build predictive models refer to patients treated with cytokines.[12–14]

To our knowledge, only a recent study had explored clinical outcomes based on the presence of bone metastases and/or liver metastases – but not other metastatic sites – in mRCC patients treated with targeted therapies (TTs).[15] In this study conducted on 2027 patients included in the International mRCC Database Consortium database, the presence of bone and liver metastases had a negative effect on survival. Therefore, the identification of novel prognostic factors from the analysis of patients treated with TTs appears warranted.

We performed a retrospective analysis of a cohort of consecutive patients who have been treated with TTs at the Istituto Nazionale Tumori (Milan, Italy), with the aim to investigate whether the metastatic site, along with other clinical parameters, is associated with progression-free survival (PFS) and OS in mRCC patients.

Patients & Methods

We retrospectively collected clinical data of 366 consecutive patients with mRCC who received TTs as first-line or subsequent treatment lines at the Istituto Nazionale Tumori between January 2005 and October 2012. The study was approved by the local ethical committee. Patients with missing data regarding both OS and PFS end points were excluded from analysis; in total, 358 (97.8%) patients were available for evaluation. All the patients had histologically proven primary RCC and had received TT within a clinical trial (EU-ARCCS,[16] TARGET,[17] AVOREN[18] or ROSORC[19]), or in a clinical practice setting. TTs included: sunitinib 50 mg orally daily (4 weeks on and 2 weeks off), sorafenib 400 mg orally twice daily, bevacizumab 10 mg/kg intravenously every 2 weeks in combination with IFN-α, pazopanib 800 mg orally daily and temsirolimus 25 mg intravenously weekly.

Statistical Methods

Baseline data were analyzed by descriptive statistics. PFS was defined as the time from the start of first-line treatment to objective tumor progression or death (which ever occurred first); the progression of disease was evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1; patients who were alive and progression-free at the time of the last contact were right censored. OS was defined as the time from the start of first-line treatment to death for any cause; patients alive or lost to follow-up at the time of the last contact were right censored. The last update was performed in December 2012.

A multivariate Cox regression model was evaluated in order to test the association between metastatic sites and PFS and OS end points, and to estimate hazard ratios (HRs). In this model, metastatic sites were categorized as the liver, lungs, brain, bone and lymph, and other sites were introduced as binary predictors.

The same multivariate model, but with the Mozter score included as an ordinal predictor, was also evaluated. An univariate Cox regression model was evaluated in order to test the statistical association between the number of metastatic sites and PFS and OS end points, and to estimate the HR; in this model, the number of metastatic sites was introduced as a continuous predictor. The same univariate model with the Mozter score added as an ordinal predictor was evaluated.

Crude survival curves were estimated using the Kaplan–Meier method; adjusted survival curves were estimated using the mean of covariates method.[20] The prevalence of each metastatic site was entered into both multivariate Cox regression models, in order to estimate the adjusted survival functions.

All statistical tests were two sided and a p-value of <0.05 was considered statistically significant. Statistical analysis was performed using the SAS software version 9.2 (SAS Institute, NC, USA); the adjusted survival functions were estimated and plotted using STATA software version 12.1 (StataCorp, TX, USA).

Results

A total of 263 (73.5%) men and 95 (26.5%) women with a median age of 61 years (range: 25–82 years) were analyzed. Metastatic lesions to the lungs were present in 237 (66%) patients; 136 (38%) patients presented with metastases to the lymph nodes, 100 (28%) patients had metastases to the bone, 63 (18%) patients had metastases to the liver, 16 (5%) had metastases to the brain and 125 (35%) patients had lesions to other sites. In total, 226 (63%) patients had metastases to more than one organ. Twenty-four patients had undergone metastectomy (22 lung and two pancreas). summarizes the clinical and pathological characteristics of the patients.

Table 1. Clinical and pathological characteristics and treatment administered.

Patients demographics	**n (%); n = 358**
Age at start of first-line treatment: – Median – Range	 61 years 25–82 years
Sex: – Males	 263 (74)

– Females	95 (26)
Performance status (Eastern Cooperative Oncology Group):	
– 0	200 (56)
– 1	135 (38)
– 2	23 (6)
Pathological characteristics	
Histology:	
– Clear cell renal carcinoma	310 (87)
– Other	48 (13)
Grade (Fuhrman):	
– 1	15 (4)
– 2	104 (29)
– 3	142 (40)
– 4	52 (14)
– Unknown	45 (13)
Risk group (Memorial Sloan–Kettering Cancer Center):	
– Low	117 (32)
– Intermediate	171 (48)
– Poor	70 (20)
Sites of metastases:	
– Lung	237 (66)
– Lymphnodes	136 (38)
– Bone	100 (28)
– Liver	63 (18)
– Brain	16 (5)
– Other[†]	125 (35)
Number of metastatic sites:	
– 1	132 (37)
– 2	132 (37)

– 3	71 (20)
– 4	18 (5)
– 5	4 (1)
– 6	1 (<1)
Treatment	
Nephrectomy:	
– Yes	312 (87)
– No	46 (13)
Number of lines of targeted therapies:	
– 1	178 (50)
– 2	113 (32)
– 3	46 (13)
– 4	19 (5)
– 5	2 (1)
Previous cytokines:	
– Yes	133 (37)
– No	225 (63)
First-line targeted agent:	
– Sorafenib	206 (58)
– Sunitinib	103 (29)
– Bevacizumab	33 (9)
– Temsirolimus	9 (3)
– Pazopanib	7 (2)

†Adrenal, soft tissue, pleural or kidney.

Progression-Free Survival & Overall Survival

After a median follow-up of 56.1 months (range: 1.0–93.2 months), 297 (83.0%) patients had progressed during first-line TT and 226 (63.3%) patients had died; median PFS was 11 months (95% CI: 8.1–12.0) and the median OS was 24.2 months (95% CI: 20.0–27.8).

Statistical Association Between PFS & Metastatic Site

The metastatic sites were statistically associated with PFS as follows: lymph nodes (HR: 1.43; 95% CI: 1.12–1.83; p = 0.004), liver (HR: 1.41; 95% CI: 1.05–1.90; p = 0.021), bone (HR: 1.26; 95% CI: 0.96–1.65; p = 0.091), brain (HR: 0.81; 95% CI: 0.46–1.43; p = 0.474) and other sites (HR: 1.07; 95% CI: 0.83–1.38; p = 0.589) (Figure 1). A significant association was detected between the number of metastatic sites and PFS (HR: 1.16; 95% CI: 1.04–1.29; p = 0.008; & Figure 2A). These relative risks translate into an absolute reduction in the median PFS of 4 months for the lymphonodes (from 12 months to 8 months), of 4.4 months for the liver (from 12 to 7.6 months) and of 3 months for the bone (from 12 to 9 months) (Figure 2).

Table 2. Statistical association between metastatic sites and progression-free survival.

Predictor	Hazard ratio; point estimate (95% CI)	p-value
Metastatic sites		
Lung: – No – Yes	 1 1.12 (0.87–1.45)	 0.364
Lymph node: – No – Yes	 1 1.43 (1.12–1.83)	 0.004
Bone: – No – Yes	 1 1.26 (0.96–1.65)	 0.091
Liver: – No – Yes	 1 1.41 (1.05–1.90)	 0.021
Brain: – No – Yes	 1 0.81 (0.46–1.43)	 0.474
Other: – No – Yes	 1 (0.29) 1.07 (83–1.38)	 0.589
Number of metastatic sites	1.16 (1.04–1.29)	0.008
Metastatic sites & Motzer score		
Lung: – No – Yes	 1 0.96 (0.74–1.24)	 0.758
Lymph node:		0.258

– No – Yes	1 1.16 (0.90–1.50)	
Bone: – No – Yes	 1 0.96 (0.73–1.27)	 0.960
Liver: – No – Yes	 1 0.94 (0.68–1.29)	 0.701
Brain: – No – Yes	 1 0.53 (0.30–0.95)	 0.033
Other: – No – Yes	 1 0.93 (0.72–1.20)	 0.589
Motzer score: – Low – Intermediate – Poor	 1 1.56 (1.18–2.07) 4.00 (2.65–6.02)	 <0.001†
Number of mestatatic sites	0.95 (0.83–1.08)	0.409
Motzer score: – Low – Intermediate – Poor	 1 1.53 (1.16–2.02) 3.78 (2.54–5.63)	 <0.001†

†Test for trend.

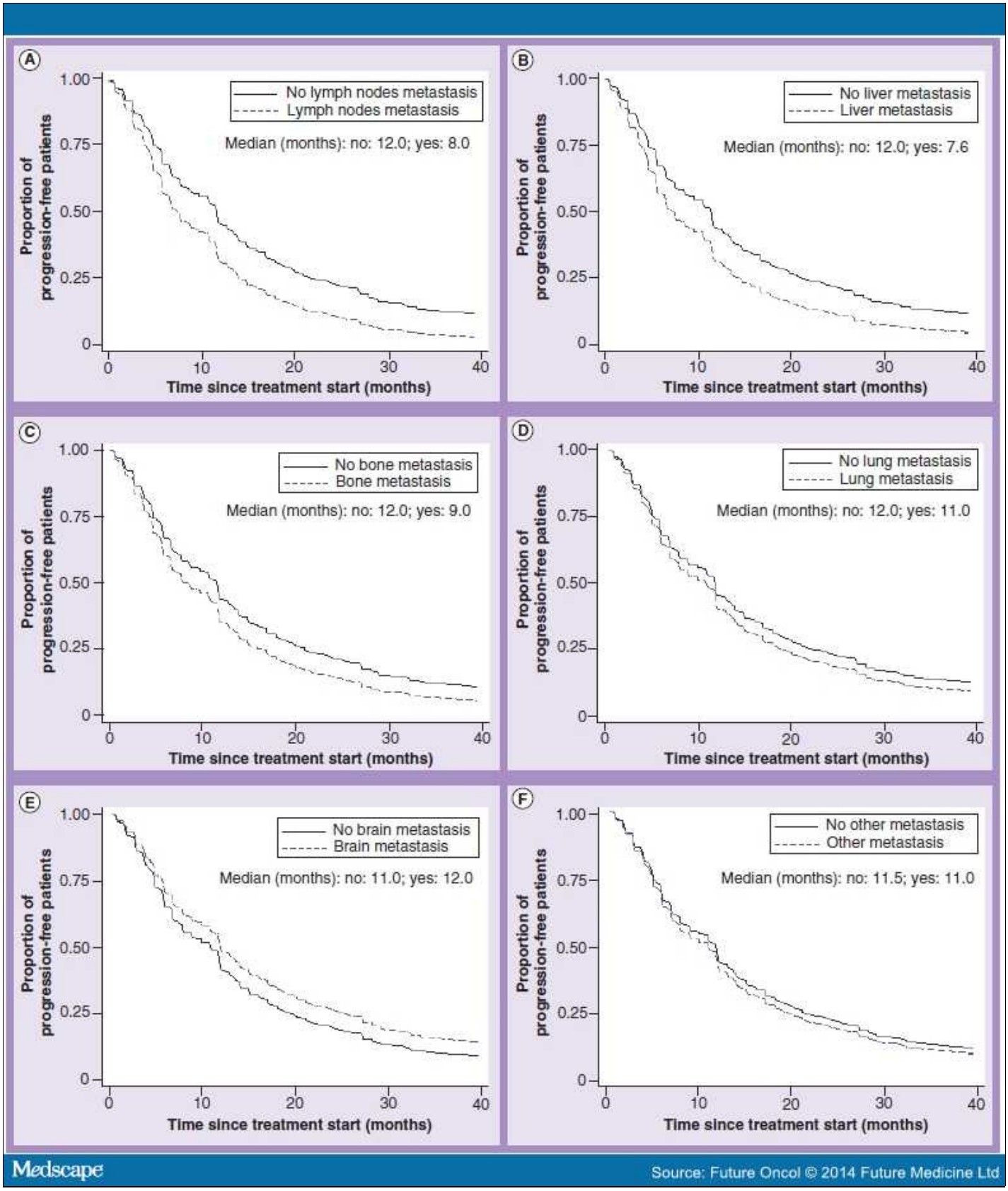

Figure 1.

Adjusted progression-free survival curves by metastatic site. (A) Lymph nodes, **(B)** liver, **(C)** bone, **(D)** lung, **(E)** brain and **(F)** other sites of metastasis.

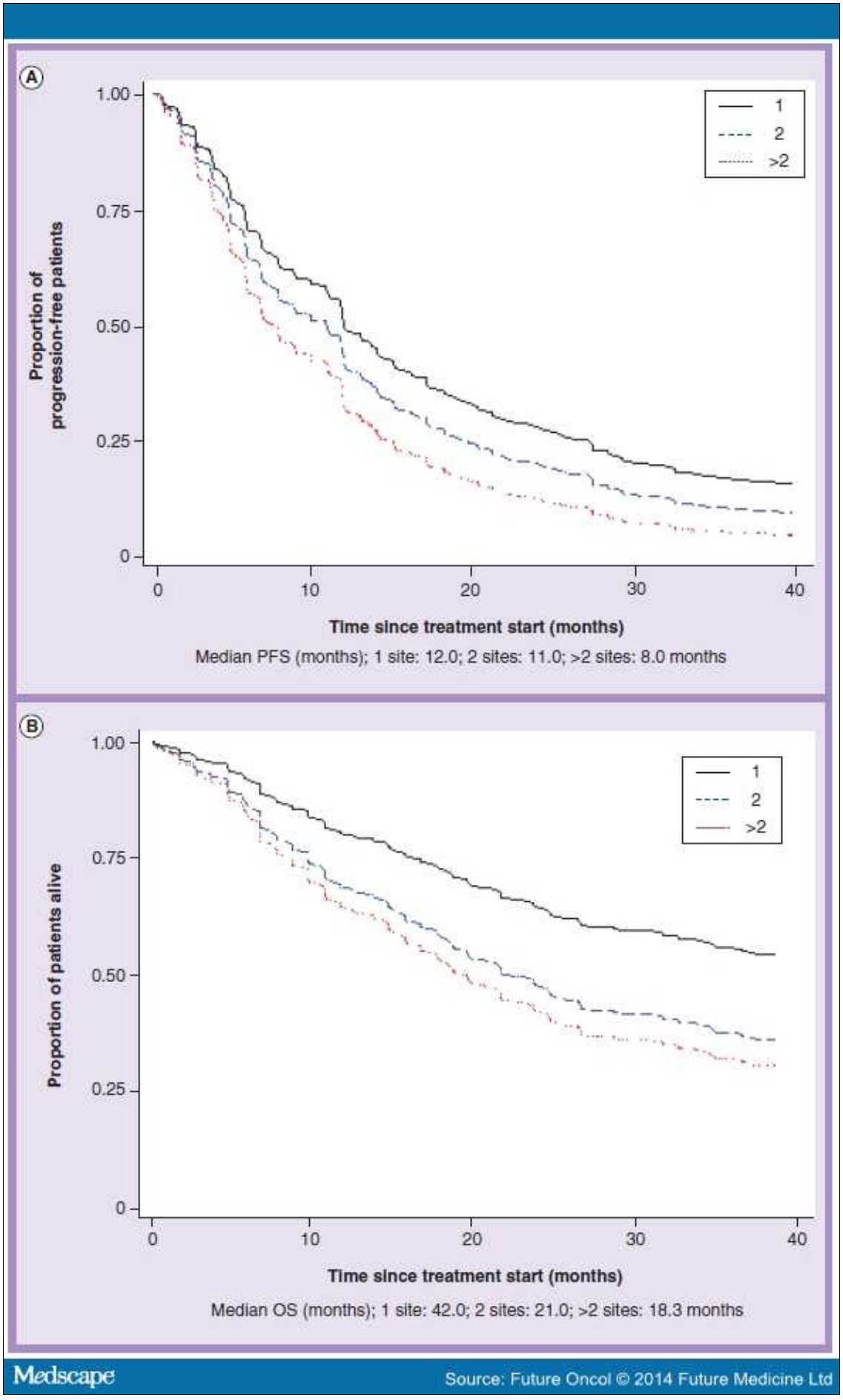
A
1.00
0.75
0.50
0.25
0
Proportion of progression-free patients
1
2
>2
0
10
20
30
40
Time since treatment start (months)
Median PFS (months); 1 site: 12.0; 2 sites: 11.0; >2 sites: 8.0 months
B
1.00
0.75
0.50
0.25
0
Proportion of patients alive
1
2
>2
0
10
20
30
40
Time since treatment start (months)
Median OS (months); 1 site: 42.0; 2 sites: 21.0; >2 sites: 18.3 months
Medscape
Source: Future Oncol © 2014 Future Medicine Ltd

Figure 2.

Progression-free survival and overall survival curves by number of metastatic sites.

Adjusted **(A)** PFS and OS **(B)** curves by number of metastatic site.

OS: Overall survival; PFS: Progression-free survival.

Statistical Association Between OS & Metastatic Site

Metastatic sites were statistically associated with OS as follows: lymph nodes (HR: 1.73; 95% CI: 1.31–2.29; p ≤ 0.001), liver (HR: 1.71; 95% CI: 1.23–2.37; p = 0.002), bone (HR: 1.48; 95% CI: 1.10–1.98; p = 0.009), brain (HR: 1.21; 95% CI: 0.64–2.28; p = 0.568) and other sites (HR: 1.09; 95% CI: 0.81–1.47; p = 0.568) (& Figure 3); a significant association was detected between the number of metastatic sites and OS (HR: 1.27; 95% CI: 1.13–1.44; p ≤ 0.001) (Figure 3B &). These relative risks translate into an absolute reduction in the median OS of 14.9 months for the lymph nodes (from 33.1 to 18.2 months), of 9.9 months for the liver (from 27.0 to 17.1 months) of 7.8 months for the bone (from 27.0 to 19.2 months) (Figure 3).

Table 3. Statistical association between metastatic sites and overall survival.

Predictor	Hazard ratio; point estimate (95% CI)	p-value
Metastatic sites		
Lung: – No – Yes	 1 1.12 (0.84–1.50)	 0.438
Lymph node: – No – Yes	 1 1.73 (1.31–2.29)	 <0.001
Bone: – No – Yes	 1 1.48 (0.10–1.98)	 0.009
Liver: – No – Yes	 1 1.71 (1.23–2.37)	 0.002
Brain: – No – Yes	 1 0.21 (0.64–2.28)	 0.568
Other:	1	0.568

– No – Yes	1.09 (0.81–1.47)	
Number of metastatic sites	1.27 (1.13–1.44)	<0.001
Metastatic sites & Motzer score		
Lung: – No – Yes	1 0.87 (0.64–1.17)	0.360
Lymph node: – No – Yes	1 1.28 (0.96–1.71)	0.095
Bone: – No – Yes	1 0.97 (0.71–1.32)	0.846
Liver: – No – Yes	1 0.98 (0.69–1.39)	0.899
Brain: – No – Yes	1 0.67 (0.35–1.28)	0.228
Other: – No – Yes	1 0.94 (0.70–1.27)	0.701
Motzer score – Low – Intermediate – Poor	1 2.02 (1.42–2.86) 7.10 (4.42–11.41)	<0.001†
Number of mestatatic sites	0.95 (0.82–1.10)	0.465
Motzer score: – Low – Intermediate – Poor	1 2.05 (1.45–2.89) 7.31 (4.64–11.53)	<0.001†

†Test for trend.

Table 3. Statistical association between metastatic sites and overall survival.

Predictor	Hazard ratio; point estimate (95% CI)	p-value
Metastatic sites		
Lung: – No – Yes	 1 1.12 (0.84–1.50)	 0.438
Lymph node: – No – Yes	 1 1.73 (1.31–2.29)	 <0.001
Bone: – No – Yes	 1 1.48 (0.10–1.98)	 0.009
Liver: – No – Yes	 1 1.71 (1.23–2.37)	 0.002
Brain: – No – Yes	 1 0.21 (0.64–2.28)	 0.568
Other: – No – Yes	 1 1.09 (0.81–1.47)	 0.568
Number of metastatic sites	1.27 (1.13–1.44)	<0.001
Metastatic sites & Motzer score		
Lung: – No – Yes	 1 0.87 (0.64–1.17)	 0.360
Lymph node: – No	 1	 0.095

– Yes	1.28 (0.96–1.71)	
Bone: – No – Yes	 1 0.97 (0.71–1.32)	 0.846
Liver: – No – Yes	 1 0.98 (0.69–1.39)	 0.899
Brain: – No – Yes	 1 0.67 (0.35–1.28)	 0.228
Other: – No – Yes	 1 0.94 (0.70–1.27)	 0.701
Motzer score – Low – Intermediate – Poor	 1 2.02 (1.42–2.86) 7.10 (4.42–11.41)	 <0.001†
Number of mestatatic sites	0.95 (0.82–1.10)	0.465
Motzer score: – Low – Intermediate – Poor	 1 2.05 (1.45–2.89) 7.31 (4.64–11.53)	 <0.001†

†Test for trend.

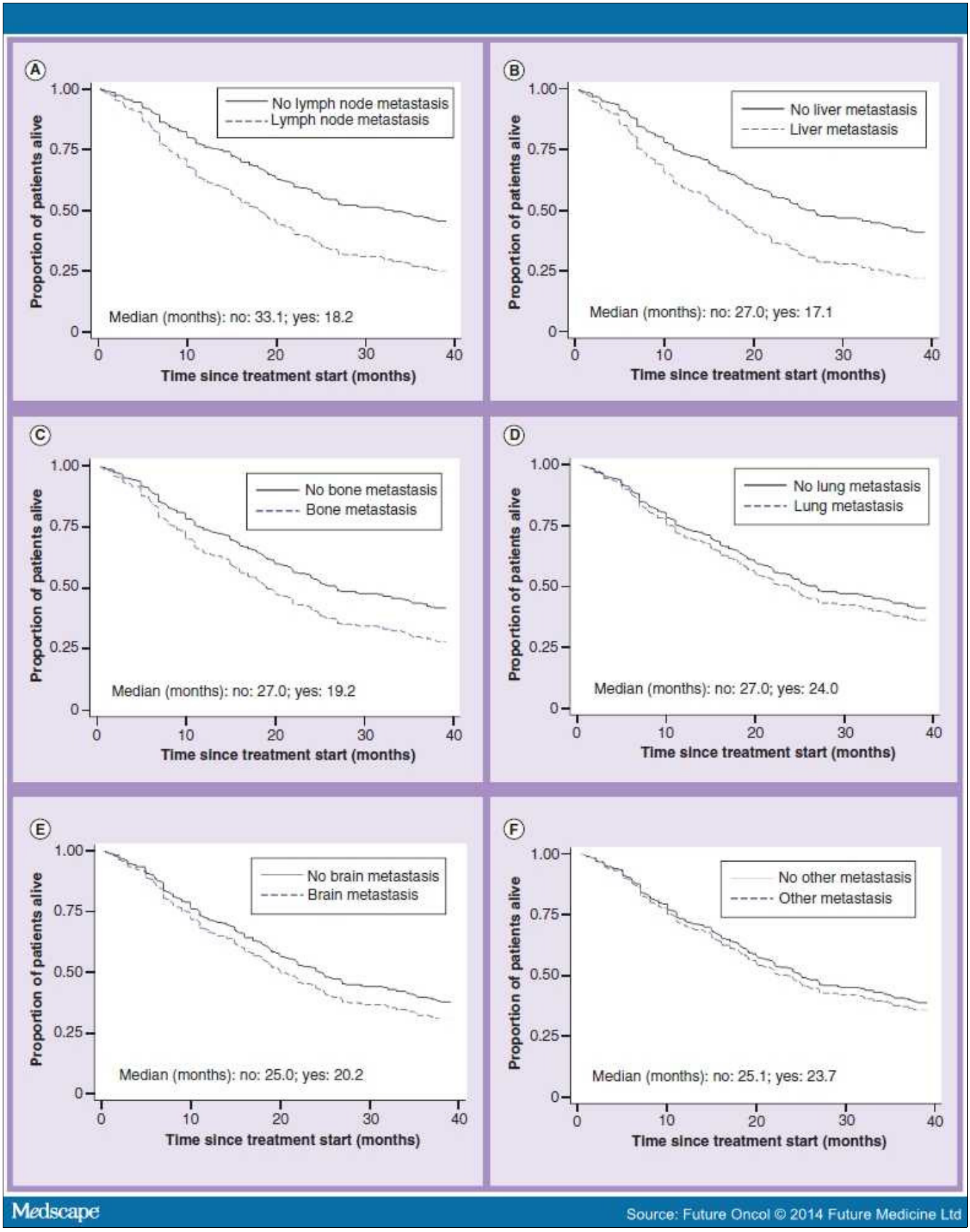
A
Proportion of patients alive
1.00
0.75
0.50
0.25
0
No lymph node metastasis
Lymph node metastasis
Median (months): no: 33.1; yes: 18.2
0
10
20
30
40
Time since treatment start (months)
B
Proportion of patients alive
No liver metastasis
Liver metastasis
Median (months): no: 27.0; yes: 17.1
Time since treatment start (months)
C
Proportion of patients alive
No bone metastasis
Bone metastasis
Median (months): no: 27.0; yes: 19.2
Time since treatment start (months)
D
Proportion of patients alive
No lung metastasis
Lung metastasis
Median (months): no: 27.0; yes: 24.0
Time since treatment start (months)
E
Proportion of patients alive
No brain metastasis
Brain metastasis
Median (months): no: 25.0; yes: 20.2
Time since treatment start (months)
F
Proportion of patients alive
No other metastasis
Other metastasis
Median (months): no: 25.1; yes: 23.7
Time since treatment start (months)
Medscape
Source: Future Oncol © 2014 Future Medicine Ltd

Figure 3.

Adjusted overall survival curves by metastatic site. **(A)** Lymph nodes, **(B)** liver, **(C)** bone, **(D)** lung, **(E)** brain and **(F)** other sites of metastasis.

Multivariate Cox Regression Models With Motzer Score as Predictor

All statistical significances were lost if the Motzer score was introduced in the PFS and OS regression models (&).

Table 2. Statistical association between metastatic sites and progression-free survival.

Predictor	Hazard ratio; point estimate (95% CI)	p-value
Metastatic sites		
Lung: – No – Yes	 1 1.12 (0.87–1.45)	 0.364
Lymph node: – No – Yes	 1 1.43 (1.12–1.83)	 0.004
Bone: – No – Yes	 1 1.26 (0.96–1.65)	 0.091
Liver: – No – Yes	 1 1.41 (1.05–1.90)	 0.021
Brain: – No – Yes	 1 0.81 (0.46–1.43)	 0.474
Other: – No – Yes	 1 (0.29) 1.07 (83–1.38)	 0.589
Number of metastatic sites	1.16 (1.04–1.29)	0.008
Metastatic sites & Motzer score		
Lung: – No – Yes	 1 0.96 (0.74–1.24)	 0.758

Lymph node: – No – Yes	 1 1.16 (0.90–1.50)	 0.258
Bone: – No – Yes	 1 0.96 (0.73–1.27)	 0.960
Liver: – No – Yes	 1 0.94 (0.68–1.29)	 0.701
Brain: – No – Yes	 1 0.53 (0.30–0.95)	 0.033
Other: – No – Yes	 1 0.93 (0.72–1.20)	 0.589
Motzer score: – Low – Intermediate – Poor	 1 1.56 (1.18–2.07) 4.00 (2.65–6.02)	 <0.001†
Number of mestatatic sites	0.95 (0.83–1.08)	0.409
Motzer score: – Low – Intermediate – Poor	 1 1.53 (1.16–2.02) 3.78 (2.54–5.63)	 <0.001†

†Test for trend.

Table 3. Statistical association between metastatic sites and overall survival.

Predictor	Hazard ratio; point estimate (95% CI)	p-value
Metastatic sites		
Lung: – No	 1	 0.438

– Yes	1.12 (0.84–1.50)	
Lymph node: – No – Yes	 1 1.73 (1.31–2.29)	 <0.001
Bone: – No – Yes	 1 1.48 (0.10–1.98)	 0.009
Liver: – No – Yes	 1 1.71 (1.23–2.37)	 0.002
Brain: – No – Yes	 1 0.21 (0.64–2.28)	 0.568
Other: – No – Yes	 1 1.09 (0.81–1.47)	 0.568
Number of metastatic sites	1.27 (1.13–1.44)	<0.001
Metastatic sites & Motzer score		
Lung: – No – Yes	 1 0.87 (0.64–1.17)	 0.360
Lymph node: – No – Yes	 1 1.28 (0.96–1.71)	 0.095
Bone: – No – Yes	 1 0.97 (0.71–1.32)	 0.846
Liver: – No	 1	 0.899

– Yes	0.98 (0.69–1.39)	
Brain: – No – Yes	 1 0.67 (0.35–1.28)	 0.228
Other: – No – Yes	 1 0.94 (0.70–1.27)	 0.701
Motzer score – Low – Intermediate – Poor	 1 2.02 (1.42–2.86) 7.10 (4.42–11.41)	 <0.001†
Number of mestatatic sites	0.95 (0.82–1.10)	0.465
Motzer score: – Low – Intermediate – Poor	 1 2.05 (1.45–2.89) 7.31 (4.64–11.53)	 <0.001†

†Test for trend.

Discussion

All the validated prognostic models for mRCC available to date take into account both patients and disease characteristics, but none consider whether the site or number of metastases can affect prognosis. The extension to two or more sites of disease were considered as a prognostic factor in the pivotal ARCCS study of temsirolimus.[16] However, in clinical practice, both the sites and the extension of disease seem to be recognized prognostic factors of the outcome in mRCC.[13,14] Recently, in a subgroup analysis of the AXIS trial that compared axitinib and sorafenib as second-line treatment for mRCC, Motzer *et al.* reported that the involvement of liver and bone was associated with a worse survival,[21] and similar findings were recently obtained in a large database study.[15] In a previous experience by our group, the presence of multiple sites of disease was associated with a poor prognosis.[10]

The main goal of the present study was to investigate the prognostic role of the different sites of disease. Multivariate analysis revealed that liver, bone and lymph nodes were prognostic factors of poor clinical outcome, since the involvement of these sites were adversely associated with PFS and OS. The poorer outcome associated with liver and bone metastasis was expected, as both sites are usually associated with a more aggressive disease, and TTs are often less effective in terms of disease control rate in patients with disease as these metastasis sites. On the other hand, the correlation between lymph nodes and worse prognosis was unexpected. In our series, the involvement of lymph nodes was documented in 38% of patients, who, in most cases, presented with metastases also at other sites: we cannot exclude that the presence of multiple metastatic sites may have contributed to the association of lymph node metastasis and poorer outcome as recently highlighted by Trinh *et al.*.[22] On the other hand, retroperitoneal lymph node involvement has been considered as an additional predictor of poor prognosis in patients treated with TTs and with primary tumor in place,[23] while the presence of both retroperitoneal and supradiaphragmatic adenopathy at the time of cytoreductive nephrectomy has been associated with poor survival.[24] Although our results are consistent with those findings, we believe that this result deserves validation in an independent sample. While in a previous study, the involvement of pancreas reported in 25 patients (7%) was a favorable prognostic feature;[25] in the present analysis, the spread of disease to the lungs, brain

and other sites was not an independent factor of clinical outcome: the lungs were the most common site of disease reported in 237 (66%) cases and lung metastases were documented in all prognostic subgroups according to the Memorial Sloan–Kettering Cancer Center criteria and were also associated with metastatic involvement of other sites in 100 cases (41%). The heterogeneity of patients affected by lung disease – who often present a number of other metastatic sites – may be a possible explanation that this site was not an independent prognostic factor. Only 16 (5%) patients had brain metastases: this low number of patients does not allow to draw any definite conclusion.

A significant correlation between number of metastatic sites and a poorer prognosis was also reported. This information may explain, at least in part, the different results obtained in terms of outcome within the same prognostic subgroup of mRCC patients reported in different clinical trials that evaluated the efficacy of TTs in terms of PFS. The survival analysis stratified for the number of sites of disease is often not performed in clinical trials, whereas it could represent an additional prognostic factor of outcome. The number of metastatic sites might be considered a surrogate of the tumor burden, which can be easily evaluated although it does not include the extension of metastases. A recent retrospective analysis reported that tumor burden – evaluated as the sum of the longest tumor diameters of the target lesions – is an independent predictive and prognostic factor in patients who started TTs.[26] Moreover, tumor burden was correlated to both the presence of symptomatic disease and the worsening of patient's performance status.[26] Importantly, we could not speculate on the influence of metastectomies on outcome, since all metastectomies in our cohort were performed on sites that are not associated with poorer outcomes.

Interestingly, the multivariate analysis could not identify metastatic sites (bone, liver and lymph node) when the Motzer score was added. However, it is important to note that the study was not prospectively planned to address the role of the Motzer score. In addition, statistical power may be markedly reduced when the Motzer score is introduced into the multivariate analysis and, therefore, statistical significance may not be reached. Larger studies are necessary to further explore this issue.

In conclusion, our study showed that patient prognosis was different according to the metastatic sites; specifically liver, bone and lymph node metastases were associated with a shorter PFS and OS. Moreover, the presence of two or more sites of disease was associated with a statistically significant shorter PFS and OS. Some limitations of our study were the retrospective nature, the heterogeneity of treatments used in different settings, such as first-line or refractory mRCC patients, and the absence of a preplanned sample size. Nevertheless, our data suggest that the sites of disease could be considered as prognostic factors: metastatic involvement of the liver, bone and lymph nodes could be considered as adverse prognostic factors of clinical outcome, as well as potential predictive factor of poor activity of TTs.

Conclusion & Future Perspective

mRCC is a heterogeneous disease. Therefore, the identification of prognostic factors able to guide therapeutic decisions is of major importance. In recent years, these factors have been incorporated into complex models, such as the Motzer criteria, which have been validated by robust studies. However, these models should be integrated with more parameters to better predict clinical outcomes.

We believe that the metastatic site can be incorporated into such models, in order to help clinicians evaluate risk and outcomes of each single patient. In the next years, prospective studies will likely be planned to address this issue, and provide clinicians with more refined prognostic models able to tailor treatment decisions on the characteristics of each single patient.

Sidebar

Executive Summary

Background

- The identification of novel prognostic factors for the analysis of patients treated with targeted therapies (TTs) is warranted.
- We performed a retrospective analysis of a cohort of consecutive patients who have been treated with TTs at the Istituto Nazionale Tumori (Milan, Italy), with the aim to investigate whether metastatic site, along with other clinical parameters, is associated with progression-free survival (PFS) and overall survival (OS) in metastatic renal cell carcinoma.

Patients & methods

- We retrospectively evaluated clinical data of 358 consecutive patients with metastatic renal cell carcinoma who received TTs

as first-line or subsequent treatment lines.

- A multivariate Cox regression model was evaluated in order to test the statistical association between metastatic sites and PFS and OS end points and to estimate hazard ratios (HRs). In this model, metastatic sites categorized as liver, lungs, brain, bone, lymph nodes and other sites were introduced as binary predictors.
- The same multivariate model, but with the Mozter score added as ordinal predictor, was also evaluated.

Results

- After a median follow-up of 56.1 months, the median PFS was 11 months and the median OS was 24.2 months.
- Some metastatic sites were significantly associated with PFS: lymph nodes (HR: 1.43; 95% CI: 1.12–1.83; p = 0.004) and liver (HR: 1.41; 95% CI: 1.05–1.90; p = 0.021).
- Some metastatic sites were significantly associated with OS: lymph nodes (HR: 1.73; 95% CI: 1.31–2.29; p < 0.001), liver (HR: 1.71; 95% CI: 1.23–2.37; p = 0.002) and bone (HR: 1.48; 95% CI: 1.10–1.98; p = 0.009).
- Patients with >2 metastatic sites had shorter PFS and OS.
- Every association was lost when introducing the Motzer score in regression models.

Discussion

- These data suggest that the sites of disease could be considered as prognostic factors: metastatic involvement of the liver, bone and lymph nodes could be considered as adverse prognostic factors of clinical outcome, as well as potential predictive factor of poor activity of TTs.

References

1. Herrmann E, Bierer S, Wulfing C. Update on systemic therapies of metastatic renal cell carcinoma. *World J. Urol.* 28, 303–309 (2010).
2. Athar U, Gentile TC. Treatment options for metastatic renal cell carcinoma: a review. *Can. J. Urol.* 15, 3954–3966 (2008).
3. Lam JS, Leppert JT, Belldegrun AS, Figlin RA. Novel approaches in the therapy of metastatic renal cell carcinoma. *World J. Urol.* 23, 202–212 (2005).
4. Cozzoli A, Milano S, Cancarini G et al. Surgery of lung metastases in renal cell carcinoma. *Br. J. Urol.* 75, 445–447 (1995).
5. Kollender Y, Bickels J, Price WM et al. Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. *J. Urol.* 164, 1505–1508 (1994).
6. Kassabian A, Stein J, Jabbour N. Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. *Urology* 56, 211–215 (2000).
7. Huisman TK, Sands JP. Renal cell carcinoma with solitary metachronous contralateral adrenal metastasis. *Urology* 38, 364–368 (1991).
8. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J. Clin. Oncol.* 17, 2530–2540 (1999).

   ** Landmark study identifies five prognostic factors for predicting survival, which can be used to categorize patients with metastatic renal cell carcinoma (mRCC) into three risk groups.
9. Mekhail TM, Abou-Jawde RM, Boumerhi G et al. Validation and extension of the Memorial Sloan–Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J. Clin. Oncol.* 23, 832–841 (2005).

   * Data reported in this paper validate the model described by Motzer *et al.* [8].

10. Procopio G, Verzoni E, Iacovelli R et al. Prognostic factors for survival in patients with metastatic renal cell carcinoma treated with targeted therapies. *Br. J. Cancer.* 107, 1227–1232 (2012).

    * Confirms the Motzer classification as an independent prognostic factor for overall survival in patients with mRCC receiving targeted therapies. Additionally, the Fuhrman grade and previous cytokine therapy were independent prognostic factors for clinical outcome.

11. Manola J, Royston P, Elson P et al. International Kidney Cancer Working Group. Prognostic model for survival in patients with metastatic renal cell carcinoma: results from the international kidney cancer working group. *Clin. Cancer Res.* 17, 5443–5450 (2011).

    ** Landmark study that identifies nine clinical factors to model survival in mRCC; the model shows utility among patients treated in the tyrosine kinase inhibitor era.

12. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res.* 48(24 Pt 1), 7310–7313 (1988).

13. Négrier S, Escudier B, Gomez F et al. Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Francais d'Immunotherapie. *Ann. Oncol.* 13, 1460–1468 (2002).

14. Ljungberg B, Landberg G, Alamdari FI. Factors of importance in prediction of survival in patients with metastatic renal cell carcinoma, treated with or without nephrectomy. *Scand. J. Urol. Nephrol.* 34, 246–251 (2000).

15. McKay RR, Kroeger N, Xie W et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. *Eur. Urol.* 65, 577–584 (2014).

16. Beck J, Procopio G, Bajetta E et al. Final results of the European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCCS) expanded-access study: a large open-label study in diverse community settings. *Ann. Oncol.* 22, 1812–1823 (2011).

17. Escudier B, Eisen T, Stadler WM TARGET Study Group. et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N. Engl. J. Med.* 356, 125–134 (2011).

18. Escudier B, Pluzanska A, Koralewski P AVOREN Trial investigators. et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind Phase III trial. *Lancet* 370, 2103–2111 (2011).

19. Procopio G, Verzoni E, Bracarda S et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. *Br. J. Cancer* 104, 1256–1261 (2011).

20. Nieto FJ, Coresh J. Adjusting survival curves for confounders: a review and a new method. *Am. J. Epidemiol.* 143, 1059–1068 (1996).

21. Motzer RJ, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised Phase 3 trial. *Lancet Oncol.* 14, 552–562 (2013).

22. Trinh QD, Sukumar S, Schmitges J et al. Effect of nodal metastases on cancer-specific mortality after cytoreductive nephrectomy. *Ann. Surg. Oncol.* 20, 2096–2102 (2013).

23. Richey SL, Culp SH, Jonasch E et al. Outcome of patients with metastatic renal cell carcinoma treated with targeted therapy without cytoreductive nephrectomy. *Ann. Oncol.* 22, 1048–1053 (2011).

24. Culp SH, Tannir NM, Abel EJ et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 116, 3378–3388 (2010).

25. Grassi P, Verzoni E, Mariani L et al. Prognostic role of pancreatic metastases from renal cell carcinoma: results from an Italian center. *Clin. Genitourin. Cancer.* 11, 484–488 (2013).

26. Iacovelli R, Lanoy E, Albiges L, Escudier B. Tumour burden is an independent prognostic factor in metastatic renal cell carcinoma. *BJU Int.* 110, 1747–1753 (2012).

Financial & competing interests disclosure

G Procopio served as a consultant for Astellas, Bayer, GSK and Pfizer. E Verzoni and R Iacovelli were consultants for Bayer and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance for the preparation of this manuscript was provided by L Giacomelli and was supported by internal funds.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Future Oncol. 2014;10(8):1361-1372.