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Kidney Cancer

Response of Primary Renal Cell Carcinoma to Systemic Therapy

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Abstract

Background: Upfront cytoreductive nephrectomy (CRN) in renal cell carcinoma (RCC) has come into question in recent prospective clinical trials.
Objective: We investigated the effect of systemic therapies on primary tumor response in patients with metastatic RCC.
Design, setting, and participants: A pooled analysis of 12 phase II/III clinical trials of metastatic RCC patients treated with systemic therapy between 2003 and 2013 was performed. Patients with one target lesion in the kidney and no prior nephrectomy were identified as having their primary tumor in place.
Outcome measurements and statistical analysis: The objective response rate (ORR) of the primary tumor was defined as per the Response Evaluation Criteria in Solid Tumors (RECIST). ORR was assessed in the overall population and patient subsets based on prior treatment and International Metastatic RCC Database Consortium (IMDC) risk group. Cox's models adjusting for baseline characteristics, treatment, line of therapy, and site of metastases were used for survival analyses.
Results and limitations: In total, 4736 patients were identified, of whom 565 had their primary tumor in place: 461 (82%) were treatment naïve, 283 (50%) received first-line vascular endothelial growth factor (VEGF)-targeted therapy, and 222 (39%) were IMDC poor risk. The ORRs of the primary tumor were 19% (95% confidence interval 16–23) in patients treated with first-line therapy (any type), 28% (22–33) in those treated with first-line VEGF-targeted therapy, and 23% (19–28) in those treated with VEGF-targeted therapy (any line). The ORRs were 9% (5–13) and 20% (15–27) in IMDC poor- and intermediate-risk patients, respectively.
Conclusions: Systemic therapy reduces primary tumor size in patients with metastatic RCC. Responses in primary tumors treated with VEGF-targeted therapy were observed in upward of 28% of patients. Selection of patients for immediate CRN requires careful consideration of patient and disease characteristics.
Patient summary: Antiangiogenic therapy meaningfully decreases the size of primary kidney tumor. Hence, for patients with metastatic disease who are not undergoing upfront cytoreductive nephrectomy, systemic therapy can palliate both primary tumor and metastases.

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1. Introduction

Approximately 62 000 new cases of renal cell carcinoma (RCC) are diagnosed every year in the USA [1]. Patients with synchronous metastases have typically been considered for cytoreductive nephrectomy (CRN) prior to systemic therapy with the intent of palliating symptomatic tumors and improving survival [2]. This practice differs from the management of most other metastatic solid malignancies, where cytoreductive surgery is not routinely offered. The benefits of CRN were attributed to negating the immunomodulatory effect of the primary tumor, rerouting immune cell away from an immunogenic primary tumor toward metastases and preventing cells to metastasize from the primary tumor [3]. The survival benefit was demonstrated in the cytokine era [4,5], prior to the approval of contemporary therapies blocking the vascular endothelial growth factor (VEGF), mammalian target of rapamycin, programmed death 1 receptor, or cytotoxic T-lymphocyte–associated protein 4 pathways [6].

The benefit of CRN in patients treated with VEGF-targeted therapy was demonstrated in two large retrospective studies from the International Metastatic RCC Database Consortium (IMDC) and the National Cancer Database, and one meta-analysis [7–9]. Randomized clinical trials investigating the efficacy of CRN in the postcytokine era were conducted mainly in Europe, but they suffered from design challenges and slow accrual [10]. SURTIME was the first trial to close and it established the safety of delayed CRN as opposed to upfront CRN [11]. It randomized clear cell RCC patients with asymptomatic primary tumors and good performance status to immediate CRN followed by sunitinib versus three cycles of sunitinib followed by CRN, and continued postoperative sunitinib. Most patients were Memorial Sloan Kettering Cancer Center (MSKCC) intermediate risk (87%). The study closed early due to poor accrual, but showed no difference in the progression-free rate at 28 wk (42% vs 43%, two-sided $p > 0.9$) and fewer surgical complications in the deferred CRN arm (28% vs 44%) [10].

The phase III non-inferiority trial CARMENA randomized patients to upfront CRN followed by sunitinib or sunitinib alone [12]. Patients had clear cell RCC with good performance status. Forty-four percent of patients in the surgical arm and 42% in the sunitinib-alone arm were MSKCC poor risk. Overall survival (OS) in the sunitinib arm was noninferior to that in the arm with upfront CRN followed by sunitinib (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.71–1.10). The trial was criticized for including many poor-risk patients, for whom CRN has a decreased benefit [9]. The high percentage of delayed CRN in the sunitinib-alone arm (17%) might have contributed to mitigating the difference between the two arms.

Collectively, these trials called into question the role and timing of CRN in metastatic RCC patients who would otherwise start immediate systemic therapy. However, the efficacy of systemic therapy in primary tumor response in the context of metastatic RCC has not been fully characterized, and it is unknown whether patients with their primary tumor in place will develop higher rates of local complications without CRN. To characterize the effect of systemic therapy on primary RCC tumors, we performed a pooled post hoc analysis of phase II/III clinical trials conducted in metastatic RCC patients during the targeted therapy era.

2. Patients and methods

2.1. Study design

This study is a pooled analysis of prospective phase II (NCT00077974, NCT00137423, NCT00267748, NCT00338884, NCT00054886, and NCT00835978) and phase III (NCT00083889, NCT00678392, NCT00920816, NCT00065468, NCT00474786, and NCT00631371) clinical trials. Studies included were conducted and sponsored by Pfizer Oncology (New York, NY, USA) between 2003 and 2013. Independent radiology review was performed for all phase III trials and one phase II trial (NCT00077974) at the time when they were conducted.

2.2. Data extraction

Data on baseline characteristics, prognostic factors, site of metastases, nephrectomy status, line of treatment, and clinical outcomes were extracted from clinical trial case report forms. Patients with primary tumors in place were identified as having one target lesion within the kidney in absence of nephrectomy. Patients with no target lesion or two or more target lesions in the kidney were not designated as having their primary tumor in place, since the determination of the primary tumor status could not be confirmed.

2.3. Statistical methods

Patient and disease baseline characteristics by cohort ("primary tumor in place" vs "others") were summarized with absolute numbers and percent. Differences between the two cohorts were analyzed using Fisher's exact test. The best response of renal target lesions was defined according to investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as a percent change in the renal target lesion largest diameter compared with baseline.

Median OS was estimated using the Kaplan-Meier method. HRs with 95% CIs and p values were obtained using Cox's models adjusting for age, gender, ethnicity, body mass index, histology (clear cell vs non–clear cell RCC), receipt of prior therapy, site of metastases, baseline IMDC risk factors (Eastern Cooperative Oncology Group [ECOG] performance status, time from diagnosis to treatment <1 yr, anemia, hypercalcemia, neutrophilia, and thrombocytosis), and neutrophil-to-lymphocyte ratio >3. To mitigate the immortal bias of responders, 6-mo landmark survival analyses were performed using a Cox proportional analysis model to compare OS in responders versus nonresponders. Patients who died within 6 mo of the start of study treatment were excluded from the landmark analyses.

All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Statistical significance was assumed at $p \leq 0.05$.

Table 1 – Baseline characteristics.

	Primary in place N = 565		Others N = 4171		*p* value
	n	%	*n*	%	
Age (yr)					
Median (IQR)	61	15	59	13	0.007
<65	367	65	2891	69	0.038
Gender					
Male	389	69	2974	71	0.2
Race					
Caucasian	433	77	3231	77	0.2
Black	13	2	63	2	
Asian	94	17	660	16	
Others or NA	25	4	217	5	
BMI					
≥25	290	51	2538	61	<0.001
Missing	9	2	70	1.7	
Baseline ECOG PS					
0	199	35	2296	55	<0.001
1	348	62	1810	43	
2	18	3	42	1	
Missing	–	–	23	1	
Histology					
Clear cell	491	87	3790	91	<0.001
Non–clear cell	30	5	322	8	
Missing	44	8	59	1	
Prior nephrectomy					
Yes	–	–	3240	78	<0.001
No	565	100	931	22[a]	
Prior therapy					
Yes	96	17	1477	35	<0.001
Missing	–	–	15	<1	
Prior cytokines					
Yes	25	4	646	15	<0.001
Prior VEGF-TKI					
Yes	28	5	545	13	<0.0001
No. of metastatic sites					
0–3	197	35	2857	68	<0.0001
>3	364	64	1241	30	
Missing	4	1	73	2	
Metastatic locations					
Bones	198	35	1103	26	<0.001
Lungs	431	76	3198	77	0.6
Liver	182	32	1056	25	0.001
Others	530	94	3258	78	<0.001
IMDC risk group					
Favorable	21	4	703	17	<0.001
Intermediate	187	33	1824	44	
Poor	222	39	923	22	
Missing	135	24	721	17	
Therapy					
Bevacizumab based	163	29	621	15	<0.001
Axitinib	61	11	835	20	
Interferon-alpha	66	12	494	12	
Sorafenib	55	10	717	17	
Sunitinib	81	14	978	23	
Temsirolimus based	139	25	526	13	

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IQR = interquartile range; NA = not available; PS = performance status; TKI = tyrosine kinase inhibitor; VEGF = vascular-endothelial growth factor.

[a] Patients with more than one kidney lesion and those with a single nontarget kidney lesion were not considered as having a primary tumor to avoid misclassification.

3. Results

A total of 4736 patients were included in the pooled analysis, of whom 565 had their primary tumor in place. Demographics and disease characteristics are presented in Table 1. Compared with the remaining of the patients, those with their primary tumor in place were more likely (≥10% difference) to have a body mass index of <25, ECOG performance status >0, no prior cytokines, less than three metastases, bone metastases, and IMDC poor-risk disease. In the cohort with primary tumor in place, 64% of patients were treated with a VEGF-targeted therapy, 25% with

Table 2 – Primary tumor best objective response rate.

	Overall		1st line (any therapy)		VEGF-targeting therapy (1st line)		VEGF-targeting therapy (any line)		International Metastatic RCC Database Consortium risk					
	N = 565		*N* = 461		*N* = 283		*N* = 360		Favorable *N* = 21		Intermediate *N* = 187		Poor *N* = 222	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%)
Objective response (95% exact CI)	94	17 (14, 20)	88	19 (16, 23)	78	28 (22, 33)	83	23 (19, 28)	9	43 (22, 66)	38	20 (15, 27)	19	8.5 (5.2, 13)
Complete response	8	1.4	7	1.5	7	2.5	8	2.2	0	–	2	1.1	1	0.5
Partial response	86	15	81	18	71	25	75	21	9	43	36	19	18	8.1
Stable disease	386	68	299	65	181	64	245	68	11	52	136	73	153	69
Progressive disease	0	–	0	–	0	–	0	–	0	–	0	–	0	–
Indeterminate	85	15	74	16	24	8.5	32	8.9	1	4.8	13	7	50	8.6

CI = confidence interval; RCC = renal cell carcinoma; VEGF = vascular-endothelial growth factor.
Indeterminate refers to patients without first response assessment on therapy.

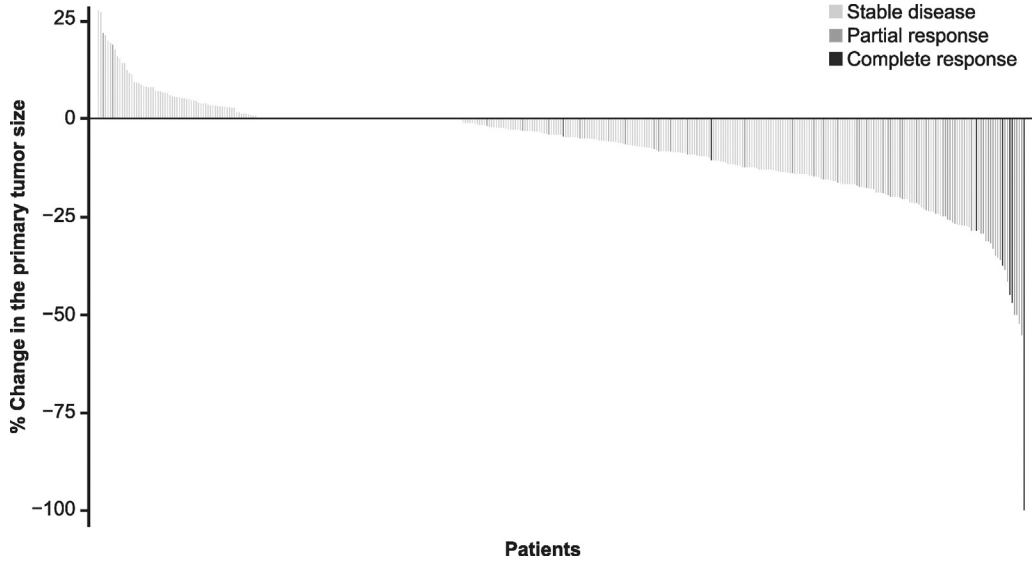

Fig. 1 – Waterfall plot showing change in primary tumor size at 6 wk of therapy.

temsirolimus-based therapy, and 12% with interferon-alpha.

3.1. Drug exposure and toxicity

In the cohort with primary tumor in place, 29% patients received bevacizumab-based treatment, 25% received temsirolimus-based treatment, 14% received sunitinib, 12% received interferon-alpha, 11% received axitinib, and 10% received sorafenib. Dose reduction or modification due to adverse events was reported in 42% (n = 136/565), whereas 17% discontinued treatment due to adverse events. At the time of the last follow-up, 68% discontinued therapy due to death, clinical progression, or radiological progression not limited to the primary tumor. Frequencies of grade 1, 2, and 3 hematuria as per the Common Terminology Criteria for Adverse Events were, respectively, 3%, 1.8%, and 1.1% in the cohort with the primary tumor in place, and 1.6%, 0.6%, and 0.1% in the cohort of other patients.

3.2. Primary tumor shrinkage

The best objective response rates (ORRs) of the primary tumor by type of therapy (VEGF-targeting therapy or any therapy), line of treatment (first line vs any line), and IMDC risk groups are summarized in Table 2. The primary tumor ORR was 17%, whereas 68% of patients had stable disease and none had progressive disease. The subgroup that received first-line VEGF-targeted therapy (n = 283) had the highest primary tumor ORR of 28%. The ORRs in IMDC intermediate- and poor-risk patients were 20% and 8.5%, respectively.

Six weeks after commencing systemic therapy, 60% (n = 322/565) of patients achieved any shrinkage in their

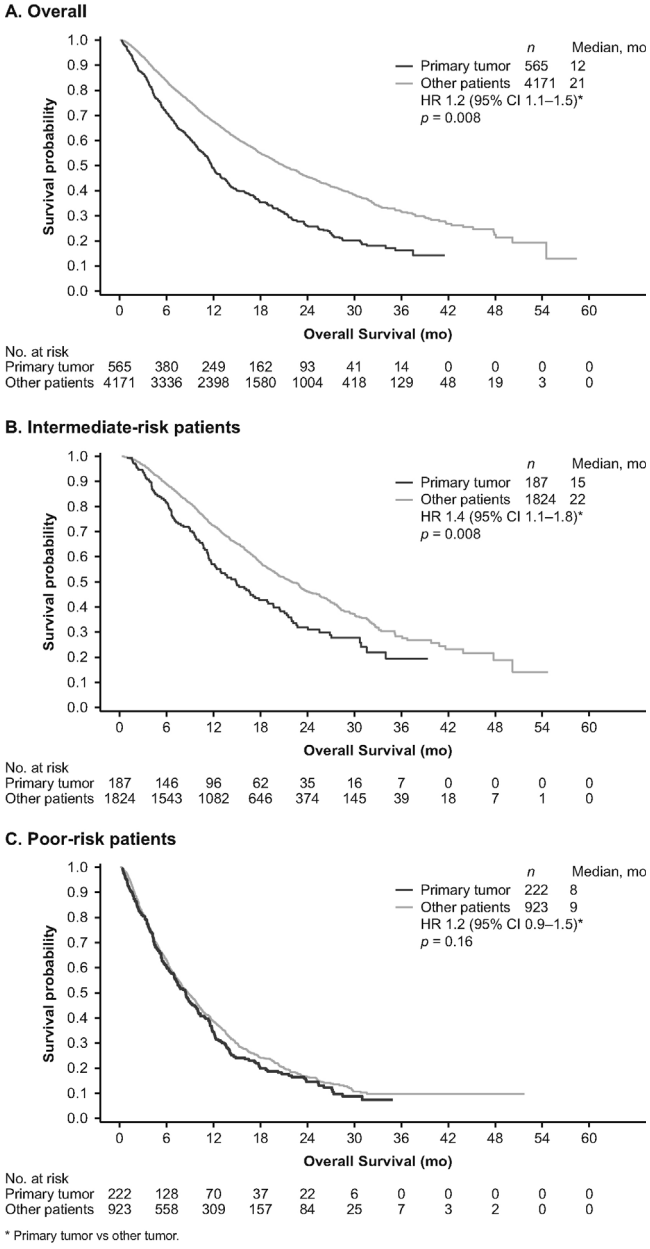

Fig. 2 – Kaplan-Meir estimates of overall survival for patients with their primary tumor in place versus other patients: (A) overall, (B) IMDC intermediate-risk patients, and (C) IMDC poor-risk patients. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

primary tumor, 67 patients (12%) had growth, and 176 (31%) did not have imaging at this time point (Fig. 1). The mean changes in tumor size at 6, 12, 18, and 24 wk were −7% (standard deviation [s.d.] 13%), −8% (s.d. 15%), −12% (s.d. 20%), and −17% (s.d. 23%), respectively. The mean maximum change in tumor size was −15% (s.d. 21%). The ORR at 3 mo was 4.8%. The median time to the best objective response was 7.5 mo.

3.3. *Survival analyses*

The median follow-up periods were 10 and 13 mo in the cohort of patient with the primary tumor in place and the other cohort, respectively. In the cohort with the primary tumor in situ, the median follow-up was 20 mo for patients who achieved an objective response and 8 mo for the nonresponders. The median follow-up for patients alive at the time of the analysis was 17.3 mo for patients with their primary tumor in place and 16.5 mo for the other patients. The median OS of patients with their primary tumor in place was 12 mo compared with 21 mo in the other cohort, corresponding to an adjusted HR of 1.2 (95% CI 1.1, 1.5; $p = 0.008$) in multivariable analysis (Fig. 2A). The difference in survival remained significant in IMDC intermediate-risk patients (adjusted HR 1.4 [95% CI 1.1, 1.8; $p = 0.008$]), whereas IMDC poor-risk patients had similar survival in both cohorts (adjusted HR 1.2 [95% CI 0.9, 1.5], $p = 0.16$; Fig. 2B and 2C).

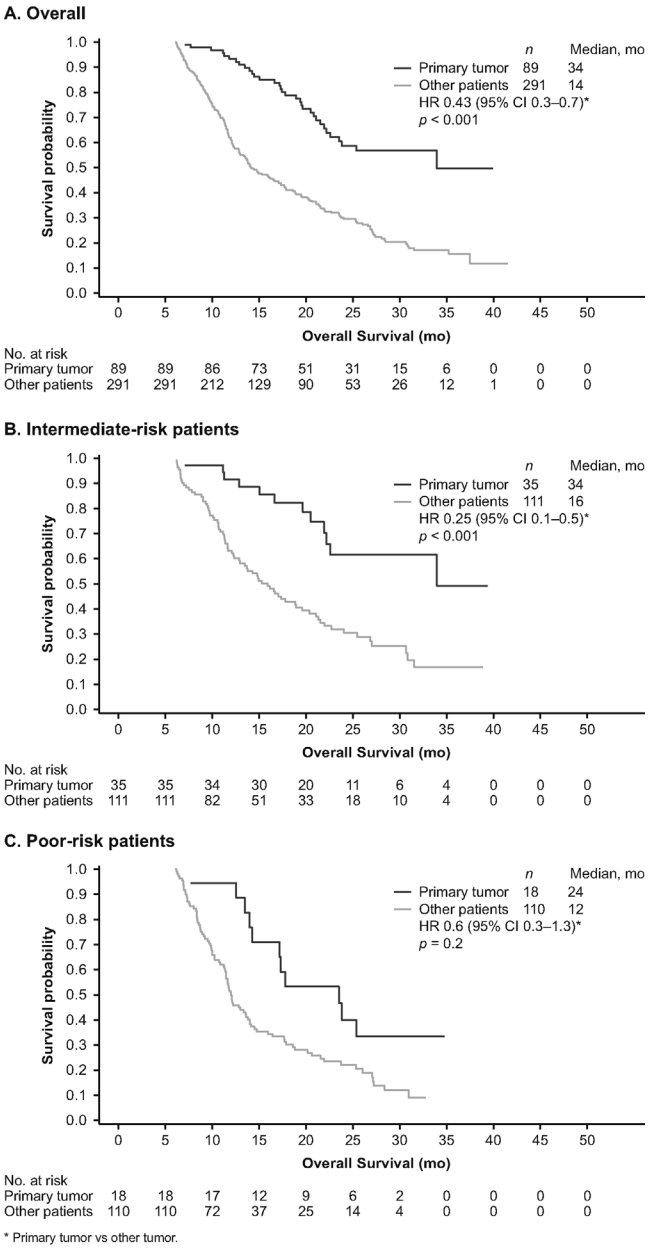

Fig. 3 – Kaplan-Meir estimates of overall survival with 6-mo landmark analysis for patients with a primary tumor objective response versus nonresponders: (A) overall, (B) IMDC intermediate-risk patients, and (C) IMDC poor-risk patients. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

A landmark survival analysis demonstrated an association between the response of the primary tumor and survival. Patients who achieved an objective response had a median survival of 34 mo compared with 14 mo in those who did not achieve an objective response (adjusted HR 0.43 [95% CI 0.3, 0.7], $p < 0.001$; Fig. 3A). The association was demonstrated in IMDC intermediate-risk patients (adjusted HR 0.25 [95% CI 0.1, 0.5; $p < 0.001$]), but did not reach statistical significance in poor-risk patients (adjusted HR 0.6 [95% CI 0.3, 1.3; $p = 0.2$]; Fig. 3B and 3C).

4. Discussion

The therapeutic landscape of metastatic RCC has evolved rapidly in the past 15 yrs. During the cytokine era, when systemic options had limited efficacy, upfront CRN improved OS and was a widely accepted paradigm in the management of metastatic patients [4,5]. Its role came into question with the approval of targeted therapies and, more recently, immune checkpoint inhibitors, With the concerns being that CRN leads to a detrimental delay of systemic therapy that would treat other sites of metastases as well as

the primary tumor. Although retrospective and real-word data suggested that CRN may still be beneficial in the postcytokine era [9], the CARMENA trial highlights that patient selection is key for determining the utility of upfront CRN and will likely temper the practice of immediate CRN [13]. However, data evaluating the impact of systemic therapy on the primary RCC tumor in the context of advanced or metastatic disease are scarce. In this study, we characterized the effect of systemic therapy on the primary tumor.

We found that upfront VEGF-targeted therapy leads to an ORR of the primary tumor of 28%, supporting the palliative role of systemic therapy in the kidney. This ORR is comparable with those reported in CARMENA and the sunitinib arm of recent first-line metastatic RCC trials [14–16], suggesting that the ORRs in the kidney mirror the overall systemic response. By comparison, Abel et al [17] previously reported a primary tumor response in a smaller and single-institution cohort of patients with RCC of any histology. The authors observed only a 5% partial response rate as per RECIST. The difference in primary tumor response in these two studies can be due to patient selection, inclusion of non–clear cell RCC in Abel et al's [17] series, different treatment exposure, and different lines of treatment.

The median time to achieve an objective response of the primary tumor was as long as 7.5 mo. Furthermore, only 4.8% achieved an objective radiological response after 3 mo of therapy. Although this long time to the best response can partly be due to the heterogeneity of therapies and lines of treatment, this rate aligns with the study of Abel et al [17], which reported a median time to maximum shrinkage of 6 mo. In another single-arm phase II trial of 104 patients who received 12–14 wk of pazopanib prior to CRN, the median shrinkage before nephrectomy was 14% [18]. In contrast, three small nonrandomized phase II trials looking at the downsizing effect of neoadjuvant axitinib, sunitinib, and pazopanib given from 12 to 16 wk prior to nephrectomy reported 46%, 25%, and 36% ORRs, respectively [19–21]. These studies differ from our cohort given that patients were all treatment naïve and did not have evidence of metastatic disease, limiting a direct comparison with our results.

Tumor biology between the primary RCC tumor and metastases may be slightly different [22]. Abbas et al [23] reported increased expression of two proangiogenic factors in metastasis compared with the corresponding primary tumor. Next-generation sequencing of matched primary and metastatic tissue samples reported discordance in gene alteration in a third of the patients [24]. Similar to the findings of de Velasco et al [25], the authors reported no unique gene alterations enriched in primary versus metastatic samples. It remains unclear whether genomic heterogeneity translates into different response profiles to targeted therapy in primary versus metastatic lesions.

As clinicians become more selective in offering immediate CRN, palliative nephrectomy may become adjunctive therapy offered later during the course of treatment [13]. This approach is safe and allows for more refined patient selection for CRN, given that CRN may not be offered to patients with RCC refractory to systemic therapy who are unlikely to benefit from it [11,18]. In our study, the ORR in the primary tumor was associated with better OS compared with the nonresponders. Of note, only 8.5% of poor-risk patients achieved an objective radiological response of their primary tumor. This subset of patients usually has a guarded prognosis and modest benefit to targeted therapy, and do not benefit from CRN [9,18,26,27]. Indeed, we found no difference in OS between poor-risk patients with their primary tumor in situ and the rest of the poor-risk patients (adjusted HR 1.18, $p = 0.17$). This finding aligns with other prospective and retrospective studies [9,12,18].

Several new drugs and immunotherapy-based combinations of treatment have recently demonstrated superior efficacy in treatment-naïve patients compared with VEGF tyrosine kinase inhibitor. In IMDC intermediate- and poor-risk patients, compared with sunitinib, both cabozantinib and the combination of ipilimumab and nivolumab improved the overall ORR [14,28]. In CheckMate-214, the ORR with ipilimumab plus nivolumab was 41% compared with 26% with sunitinib, and the complete response rate was 11% versus 1% [29]. Likewise, superior overall ORRs were observed with the combinations of axitinib plus pembrolizumab (59% vs 36%) and axitinib plus avelumab (51% vs 26%) compared with sunitinib in the Keynote-426 and Javelin Renal-101 trials, respectively [30,31]. The rates of prior nephrectomy in these front-line trials were 83% for Keynote-426, 80% for Javelin-Renal 101, and 81% for CheckMate-214. The direct impact of these immunotherapy combinations on the response rate of the primary tumor in patients without a prior nephrectomy has not been characterized fully. Additionally, the rate of prior nephrectomy in patients with a complete response is not specified in these studies.

The study limitations are the following. Patients with their primary tumor in place, compared with the cohort of other patients, have numerous adverse clinical features such as bone and liver metastases, which are associated with decreased benefit of therapy and shorter survival [32]. The nephrectomy status of the cohort of other patients did not allow for differentiating between partial and radical nephrectomy. The database does not include patients receiving more recently approved agents such as checkpoint inhibitors. The clinical activity of these treatments may be different from what we report herein. The study population included in our pooled analysis was derived from clinical trials, and findings may not be completely generalizable to nonclinical trial population. The radiological response assessment reported in some of the trials pooled in this study was investigator assessed. Lastly, some patients with their tumor in situ may have been classified in the cohort of other patients if they did not meet our definition.

5. Conclusions

Antiangiogenic therapy is effective for the primary tumor and leads to significant downsizing in up to 28% of patients. While the best objective response takes on average 7.5 mo to occur, frank progression of the primary tumor on treatment does not occur frequently. As the treatment

landscape of metastatic RCC continues to evolve toward more efficacious upfront treatments, palliation of the primary tumor with systemic therapy is also likely to improve.

Author contributions: Rana R. McKay 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: Bossé, Simantov, Choueiri, McKay.
Acquisition of data: Lin, Simantov.
Analysis and interpretation of data: Bossé, Lin, Choueiri, McKay.
Drafting of the manuscript: Bossé, Choueiri, McKay.
Critical revision of the manuscript for important intellectual content: Bossé, Lin, Simantov, Lalani, Derweesh, Chang, Choueiri, McKay.
Statistical analysis: Lin.
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Administrative, technical, or material support: Choueiri, Lin, Simantov.
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Other: None.

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