

European Association of Urology

Kidney Cancer

Effect of Inferior Vena Cava Tumor Thrombus on Overall Survival in Metastatic Renal Cell Carcinoma Patients Treated with Cytoreductive Nephrectomy

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Article info

Article history:

Accepted August 5, 2022

Associate Editor:

M. Carmen Mir

Keywords:

Metastatic renal cell carcinoma
Cytoreductive nephrectomy
Inferior vena cava thrombus
Renal vein thrombus

Abstract

Background: Survival data regarding cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC) patients according to the type and extent of tumor-associated vascular thrombus are scarce.

Objective: To test for survival differences in mRCC patients treated with CN according to the type and extent of tumor-associated vascular thrombus.

Design, setting, and participants: Within Surveillance, Epidemiology, and End Results Research Plus (2004–2017), we identified CN mRCC patients with renal vein (pT3a-TT) versus infradiaphragmatic inferior vena cava (IVC; pT3b) versus supradiaphragmatic IVC tumor thrombus/IVC invasion (pT3c).

Outcome measurements and statistical analysis: Overall survival (OS) was addressed in Kaplan-Meier and Cox regression analyses, in addition to 3-mo landmark analyses.

Results and limitations: Of 2170 mRCC patients, 1880 (87%), 204 (9%), and 86 (4%) harbored pT3a-TT, pT3b, and pT3c, respectively. The respective median OS periods were 21, 23, and 12 mo ($p < 0.001$). In multivariable Cox regression models, pT3c stage, but not pT3b stage, was an independent predictor of higher overall mortality (hazard

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ratio [HR]: 1.37; 95% confidence interval [CI]: 1.09–1.73; $p = 0.007$), as well as in 6-mo landmark analyses (HR: 1.36; 95% CI: 1.02–1.80; $p = 0.04$). In the sensitivity analysis, relying on all pT3a patients, the predictor status of pT3c stage remained unchanged (HR: 1.37; 95% CI: 1.09–1.71; $p = 0.007$). Limitations have to be addressed regarding the sample size and the retrospective design of the current study.

Conclusions: Although overall mortality is significantly higher in pT3c mRCC patients than in their pT3b and pT3a-TT counterparts, these individuals may still expect 12-mo or better OS after CN versus virtually 2-yr OS in their pT3a and pT3b counterparts.

Patient summary: In this study, we looked at the survival outcomes of metastatic renal cell carcinoma patients who presented with tumor thrombus at cytoreductive nephrectomy. Even though these patients with most advanced tumor thrombus stage demonstrated lower survival rates, the median overall survival was still 1 yr.

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1. Introduction

Metastatic renal cell carcinoma (mRCC) patients with either renal vein or inferior vena cava (IVC) tumor thrombus and cytoreductive nephrectomy (CN) represent a rare entity [1]. Existing data originate predominantly from one multi-institutional and one population-based study [1–3]. Here, one descriptive, multi-institutional study reported by Abel et al. [2] addressed this specific patient population: pT3a ($n = 257$), pT3b ($n = 130$), and pT3c ($n = 40$). Specifically, Abel et al. [2] demonstrated that supradiaphragmatic IVC tumor thrombus (pT3c) purported worse overall survival (OS) than infradiaphragmatic IVC tumor thrombus (pT3b) or renal vein tumor thrombus (pT3a) at CN. Conversely, Lenis et al. [3] relied on the National Cancer Database. Their sample size of CN mRCC patients was considerable (pT3a: $n = 1,460$; pT3b: $n = 287$; pT3c: $n = 87$); however, a specific comparison according to pT3 substages was not provided [3]. Finally, five, even smaller scale, single-institution studies provided additional observational data. However, these were severely limited by their sample size ($n = 15–111$) [4–9]. To address the existing knowledge gap, we attempted to provide additional, large-scale observations testing for OS differences according to pT3 substages in CN mRCC patients. We hypothesized that similar OS estimates to those reported by Abel et al. [2] will be identified. We addressed these hypotheses using the Surveillance, Epidemiology, and End Results Research Plus (SEER) database (2004–2017) [10].

2. Patients and methods

2.1. Study population

The current SEER database samples 34.6% of the US population and approximates it in demographic composition and cancer incidence [10]. Within the SEER database 2004–2017, we identified all patients ≥ 18 and ≤ 75 yr of age with histologically confirmed, metastatic (clinical or pathological) renal cell carcinoma (International Classification of Disease for Oncology site code C64.9). Histological subtypes according to the 2016 World Health Organization and Heidelberg classification included clear cell renal cell carcinoma ([ccRCC] code 8310), non-clear cell renal cell carcinoma ([non-ccRCC] papillary and chromophobe, code 8260 and 8317), and mRCC histology with unknown further histological classification ([unknownRCC] code 8312) [10–13]. Of these patients, CN-

treated patients with renal vein tumor thrombus (pT3a-TT; CS-extension code: 601), infradiaphragmatic IVC tumor thrombus (pT3b; CS-extension code: 610), supradiaphragmatic IVC tumor thrombus/IVC wall infiltration (CS-extension code: 620), or IVC tumor thrombus not specified further (pT3NOS; CS-extension code: 625), adapted from the seventh American Joint Committee on Cancer staging system, represented the current study population [10,14]. Patients with pT3NOS ($n = 101$) were excluded from further analyses. Moreover, in sensitivity analyses, we relied on all pT3a mRCC patients (pT3a; CS-extension codes: 400, 450, 460, 600, 601, and 605), instead of only mRCC patients with renal vein tumor thrombus (pT3a-TT) [10,14]. Patients with unknown lymph node dissection status (defined as missing information regarding lymph node yield [unknown]; $n = 10$) or bilateral renal cell carcinoma ($n = 11$) were excluded. Overall mortality (OM) was defined as death, irrespective of the underlying cause. Follow-up was defined as time from diagnosis to the end of study period, loss to follow-up, or death.

2.2. Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges were reported for continuously coded variables. The chi-square test examined the statistical significance of the differences in proportions, while the Kruskal-Wallis test was used to examine differences in medians.

Specific statistical analyses consisted of three parts. In the first part of the analysis, the study population was stratified according to the presence of renal vein tumor thrombus (pT3a-TT) versus infradiaphragmatic IVC tumor thrombus (pT3b) versus supradiaphragmatic IVC tumor thrombus/IVC wall invasion (pT3c). We relied on Kaplan-Meier plots and Cox regression analyses to test for OM differences according to tumor thrombus substages (pT3a-TT vs pT3b vs pT3c). Adjustment variables consisted of age at diagnosis (continuously coded), tumor size (per 10 mm), pN stage (N0 vs N1 vs Nx), histology type (ccRCC vs non-ccRCC vs unknownRCC), histology grade (G1–2 vs G3–4 vs Gx), presence of sarcomatoid features (no vs yes vs unknown), and year of diagnosis (continuously coded). Moreover, additional treatment modalities (radiotherapy, systemic therapy, and metastasectomy) were adjusted for (no vs yes) without further stratification according to the time of administration (upfront vs deferred relative to CN).

In the second part of the analyses, landmark analysis was performed at 6 mo, beginning from the date of CN, as described previously. Subsequently, Kaplan-Meier plots and Cox regression analyses were refitted. Same adjustment covariates as above were used.

In the third and final part, sensitivity analyses focused on the overall cohort of pT3a mRCC patients, instead of only mRCC with renal vein tumor thrombus (pT3a-TT). Relying on this fully inclusive group of

pT3a mRCC patients, Kaplan-Meier and Cox regression analyses, addressing OS, were refitted without and subsequently with 6-mo landmark analyses.

All tests were two sided with a level of significance set at $p < 0.05$, and R software environment for statistical computing and graphics (version 4.1.1) was used for all analyses [15].

3. Results

3.1. Descriptive characteristics according to pT3 substages

Of 2170 eligible patients with the presence of tumor thrombus, 1880 (87%), 204 (9%), and 86 (4%) harbored renal vein tumor thrombus (=pT3a-TT), infradiaphragmatic IVC tumor thrombus (=pT3b), and supradiaphragmatic IVC tumor thrombus/IVC wall invasion (=pT3c), respectively (Table 1). Tumor size was 97 versus 105 versus 103 mm, rate of pN1 stages was 24% versus 33% versus 33%, and the rate of sarcomatoid feature was 15% versus 23% versus 10% in pT3a-TT versus pT3b versus pT3c (all $p < 0.05$; Table 1). No statistically significant differences were recorded for histological type, histological grade, and rates of metastasectomy and systemic therapy within the subgroups (both $p > 0.05$).

3.2. OM according to tumor thrombus extent regarding pT3 substages

The median OS was 21 versus 23 versus 12 mo for pT3a-TT versus pT3b versus pT3c CN mRCC patients (Fig. 1A). In Cox regression analyses testing for OM differences, solely pT3c stage (reference [Ref]: pT3a-TT), but not pT3b stage, was a

statistically significant predictor of higher OM in both univariable (hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.18–1.86) and multivariable (HR: 1.37; 95% CI: 1.09–1.73) analyses (both $p < 0.05$; Table 2). In 6-mo landmark analyses, 1688 patients remained for further analyses (pT3a: $n = 1473$; pT3b: $n = 157$; pT3c: $n = 58$). In refitted Cox regression models, solely pT3c stage (Ref: pT3a-TT) was an independent, statistically significant predictor of OM in multivariable (HR: 1.36; 95% CI: 1.02–1.80; $p = 0.04$) analyses (Fig. 1B and Table 2).

3.3. OM sensitivity analyses including all pT3a patients

Relying on all pT3a patients (Supplementary Table 1), instead of only mRCC with renal vein tumor thrombus (pT3a-TT), resulted in a cohort of 3421 CN mRCC patients: pT3a: 3122 (91%), pT3b: 204 (6%), and pT3c: 86 (2%). Here, the median survival was 19 versus 23 versus 12 mo for pT3a versus pT3b versus pT3c CN mRCC patients (Fig. 2A). In Cox regression analyses testing for OM differences, solely pT3c stage (Ref: pT3a), but not pT3b stage, was a statistically significant predictor of higher OM in both univariable (HR: 1.41; 95% CI: 1.12–1.76) and multivariable (HR: 1.37; 95% CI: 1.09–1.71) analyses (both $p < 0.05$; Table 3).

In 6-mo landmark analyses, 2629 patients remained for further analyses (pT3a: $n = 2414$; pT3b: $n = 157$; pT3c: $n = 58$). In refitted Cox regression models, solely pT3c stage (Ref: pT3a) was an independent, statistically significant predictor of OM in multivariable (HR: 1.34; 95% CI: 1.01–1.77; $p = 0.04$) analyses (Fig. 2B and Table 3).

Table 1 – Descriptive characteristics of 2170 metastatic kidney cancer patients (pT3a-TT vs pT3b vs pT3c) treated with cytoreductive nephrectomy within the Surveillance, Epidemiology, and End Results Research Plus data repository between 2004 and 2017

	N = 2170	pT3a-TT (N = 1880; 87%)	pT3b (N = 204; 9.4%)	pT3c (N = 86; 4.0%)	p value ²
Age (yr), median (IQR)	60 (53, 66)	60 (53, 66)	60 (53, 66)	61 (56, 68)	0.3
Tumor size (mm), median (IQR)	100 (75, 124)	97 (75, 120)	105 (84, 135)	103 (84, 135)	<0.001
Gender, n (%)					0.6
Female	614 (28)	537 (29)	52 (25)	25 (29)	
Male	1556 (72)	1343 (71)	152 (75)	61 (71)	
Race/ethnicity, n (%)					0.3
Caucasian	1551 (71)	1351 (72)	135 (66)	65 (76)	
African American	144 (6.6)	117 (6.2)	19 (9.3)	8 (9.3)	
Hispanic	306 (14)	265 (14)	32 (16)	9 (10)	
Other	169 (7.8)	147 (7.8)	18 (8.8)	4 (4.7)	
pN stage, n (%)					<0.001
N0	621 (29)	516 (27)	82 (40)	23 (27)	
N1	523 (24)	448 (24)	47 (23)	28 (33)	
Nx	1026 (47)	916 (49)	75 (37)	35 (41)	
Histology, n (%)					>0.9
Clear cell	1551 (71)	1348 (72)	144 (71)	59 (69)	
No clear cell	283 (13)	243 (13)	29 (14)	11 (13)	
Unknown	336 (15)	289 (15)	31 (15)	16 (19)	
Grade, n (%)					0.07
G1–2	285 (13)	255 (14)	18 (8.8)	12 (14)	
G3–4	1769 (82)	1529 (81)	174 (85)	66 (77)	
GX	116 (5.3)	96 (5.1)	12 (5.9)	8 (9.3)	
Sarcomatoid feature, n (%)					<0.001
No	1032 (48)	856 (46)	147 (72)	29 (34)	
Yes	334 (15)	279 (15)	46 (23)	9 (10)	
Unknown	804 (37)	745 (40)	11 (5.4)	48 (56)	
Systemic therapy, n (%)	1134 (52)	992 (53)	106 (52)	36 (42)	0.2
Radiotherapy, n (%)	507 (23)	461 (25)	32 (16)	14 (16)	0.005
Metastasectomy, n (%)	382 (18)	317 (17)	44 (22)	21 (24)	0.06

G = grade; IQR = interquartile range; TT = tumor thrombus.
All values are median (IQR) or frequencies (%).

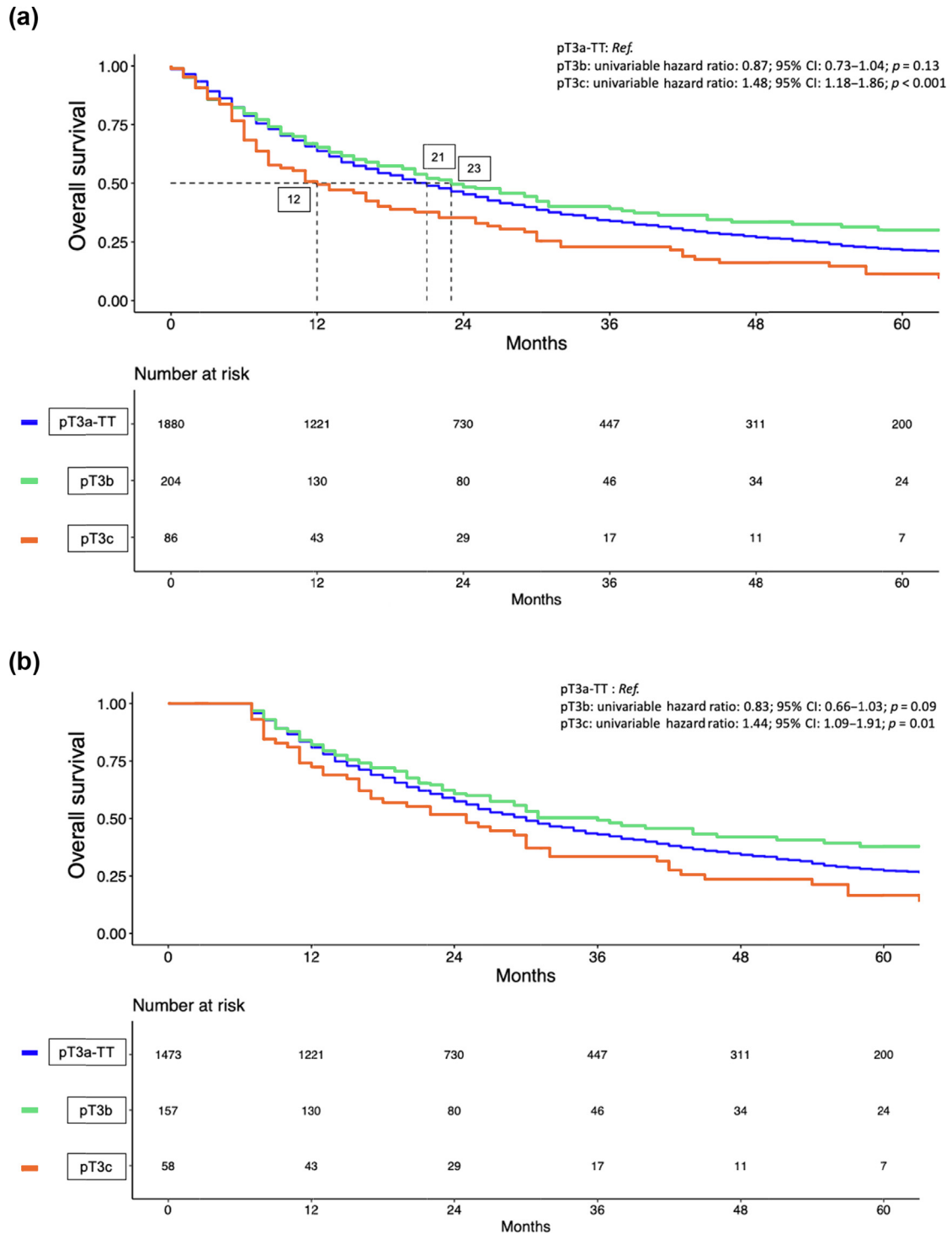


Figure 1 – Kaplan-Meier plots illustrating overall survival in (A) 2171 metastatic kidney cancer (mRCC) patients (pT3a-TT vs pT3b vs pT3c) treated with cytoreductive nephrectomy and (B) 1919 mRCC patients with a 3-mo landmark analysis within the Surveillance, Epidemiology, and End Results (SEER) Research Plus data repository between 2004 and 2017. CI = confidence interval; Ref. = reference; TT = tumor thrombus.

4. Discussion

Metastatic renal cell carcinoma patients with either renal vein or IVC tumor thrombus and CN represent a rare entity. Our objective was to provide additional observations for the rarity of CN mRCC patients with renal vein, infradiaphrag-

matic, or supradiaphragmatic IVC tumor thrombus. To address this void, we relied on CN-treated mRCC from within the SEER database between 2004 and 2017, and made several noteworthy findings [10].

First, within all mRCC patients treated with CN, the presence of tumor thrombus within the vascular system,

Table 2 – Univariable and multivariable Cox regression models predicting overall mortality of metastatic kidney cancer patients (pT3a-TT vs pT3b vs pT3c) treated with cytoreductive nephrectomy within the Surveillance, Epidemiology, and End Results Research Plus data repository between 2004 and 2017, before and after 6-mo landmark analyses

		Univariable Cox regression			Multivariable Cox regression		
		Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Without 6-mo landmark (n = 2170)	pT stage (Ref: pT3a-TT)	Ref			Ref		
	pT3b	0.87	0.73–1.04	0.13	0.93	0.77–1.12	0.45
	pT3c	1.48	1.18–1.86	<0.001	1.37	1.09–1.73	0.007
With 6-mo landmark (n = 1688)	pT stage (Ref: pT3a-TT)	Ref			Ref		
	pT3b	0.83	0.66–1.03	0.09	0.88	0.70–1.11	0.29
	pT3c	1.44	1.09–1.91	0.01	1.36	1.02–1.80	0.04

CI = confidence interval; Ref = reference; TT = tumor thrombus.

namely, renal vein or IVC, was found in a non-negligible proportion of patients. Specifically, 2170 (38%) of all 5676 CN-treated mRCC within the current study population harbored either renal vein or IVC involvement at final pathological examination. However, the vast majority of such patients present with pT3a(-TT) followed by pT3b patients, and only a small fraction harbor supradiaphragmatic tumor thrombus or IVC wall invasion (pT3c). For example, Abel et al. [2] described only 40 pT3c CN patients within their multi-institutional series. In the current study, more than twice that number (n = 86) was identified [2]. Even though the presence of tumor thrombus varied within other more historical, smaller-scale, single-institution case series (range: 23–59%), the results of the current study clearly indicate that a large proportion of CN patients harbor vascular tumor thrombus [6,7,16]. In consequence, additional large-scale, epidemiological data regarding this important subgroup of CN patients are clearly needed to address the important knowledge gap regarding eligibility for CN and cancer control outcomes after CN.

We addressed some of these limitations in the second part of the analyses. Specifically, we examined OS differences associated with specific levels and/or tumor thrombus invasion. Here, we tested for OS focusing on the most advanced substage of the pT3 cohort, harboring supradiaphragmatic IVC tumor thrombus and/or IVC wall invasion, namely, pT3c. Our intent was to test whether the recorded OS in this particularly advanced pT3c subgroup was clinically meaningful and justifies CN. In the current analyses, the median OS was expectedly lowest in pT3c patients (12 mo) and increased to 23 and 21 mo in, respectively, pT3b and pT3a-TT patients ($p < 0.05$). In consequence, the eligibility criteria for CN based on clinical considerations were met not only in the most favorable pT3 stage (pT3a-TT), but also in the intermediate group of pT3b and in the most unfavorable group of pT3c patients. These observations represent helpful data when decisions regarding CN in mRCC patients with involvement of the vascular system are evaluated.

Last but not least, we expanded hypothesis testing about OS in pT3 substages of CN mRCC patients to include all pT3a individuals, not only those with pT3a-TT substage, who were limited to patients with renal vein tumor thrombus [14]. Here, a notably larger pT3a group was included that consisted of 3421 pT3a mRCC patients. Relying on this larger group of pT3a CN mRCC patients, we recorded virtually the same median OS values in pT3a versus pT3b versus pT3c CN mRCC patients (Fig. 2). Additionally, pT3c-stage CN patients also exhibited the worst OS, relative to their pT3b

and pT3c counterparts. Moreover, and in line with the main analysis, pT3 stage remained an independent predictor for higher OM in Cox regression analyses (Table 3).

Taken together, these observations indicate that pT3c patients indeed exhibit worse OS than pT3a and pT3b counterparts after CN. However, even in pT3c CN mRCC patients, recorded OS meets clinically meaningful median OS of 12 mo. In consequence, even in pT3c patients, CN may appear justifiable [17,18]. The current findings are in agreement with results reported by Abel et al. [2] who relied on a multi-institutional cohort of CN mRCC patients with tumor thrombus [3]. However, in the Abel et al.'s [2] study, the median OS in pT3c patients was shorter (9 mo) than in the current study (12 mo). Conversely, in pT3a and pT3b patients, OS values recorded by Abel et al. [2] were in close agreement with the current OS values [3]. It is of note that the current findings are in contrast to Abel et al.'s [2] study based on a two-fold larger number of pT3c patients. Additionally, the somewhat more favorable median OS in pT3c patients within the current population-based study, relative to the Abel et al.'s [2] center of excellence study, suggests that at least comparable survival after CN may be expected in pT3 patients treated predominantly outside of centers of excellence [3].

To the best of our knowledge, no other sufficiently numbered study addressed the same concepts as those reported by Abel et al. [2] and the current study. In consequence, no study may directly be compared with the study by Abel et al. [2] or the current study. Nonetheless, others examined survival outcomes in pT3 substages treated with CN. However, a lack of information regarding pT3 substages or different study design concepts renders a direct comparison with the current study [3,19,20]. For example, Lenis et al. [3] focused on the comparison between CN and no-CN mRCC patients and included pT3 patients. This design difference (CN vs no CN) makes comparisons with studies such as that of Abel et al. [2] and the current study impossible, since absolute data are not provided. Instead, comparison is made after propensity score matching where similar patient characteristics are used for the inclusion of CN and of no-CN patients. Such selection renders median OS values uninterpretable [3].

Finally, it must be highlighted that the current study population represents a rare, yet challenging, subgroup of mRCC patients when CN is undertaken. Assessment and perioperative risk management as well as defining the most appropriate surgical approach (open vs laparoscopic vs robotic assisted) for each patient individually, represent

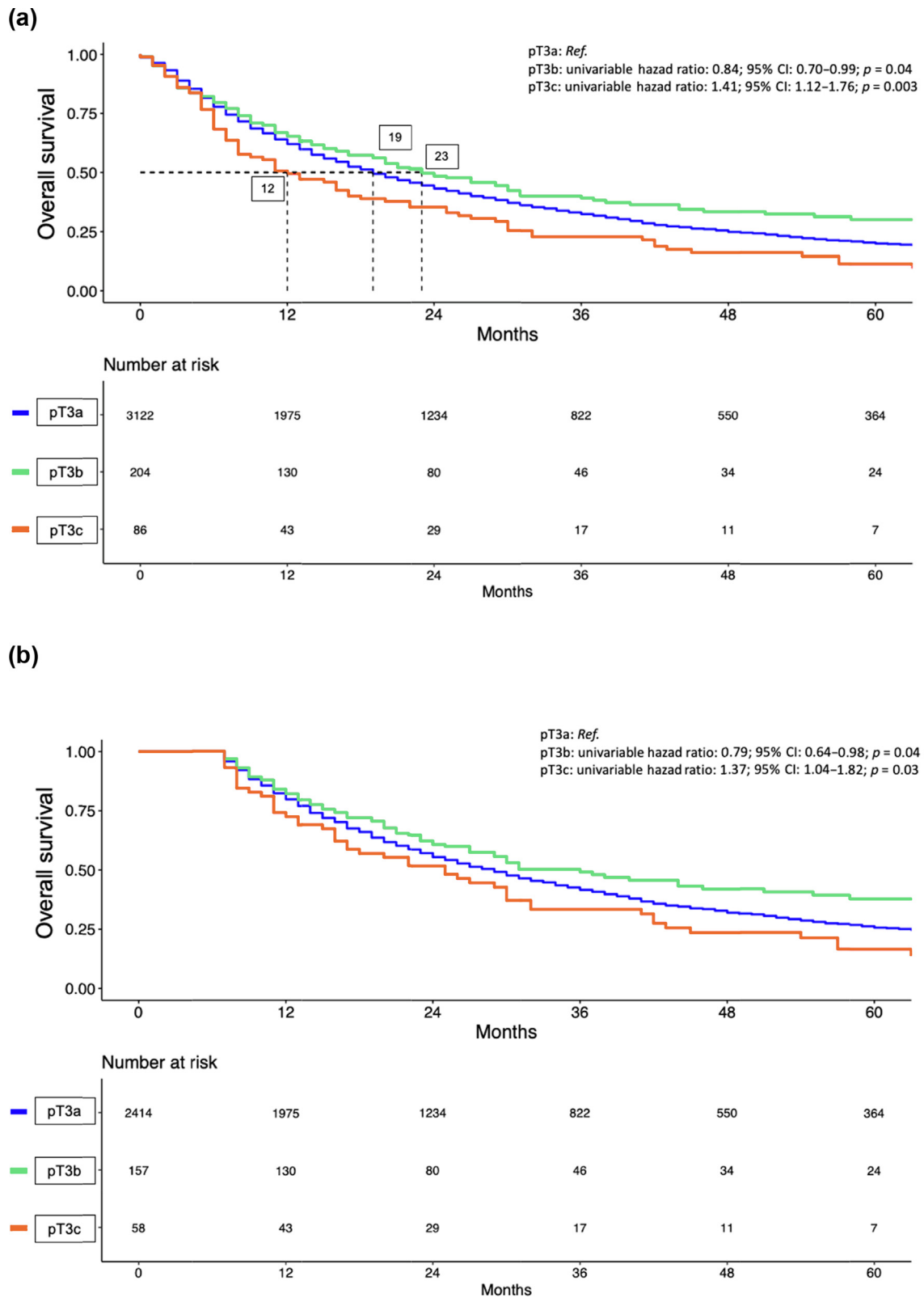


Figure 2 – Kaplan-Meier plots illustrating overall survival in (A) 3415 metastatic kidney cancer (mRCC) patients (pT3a vs pT3b vs pT3c) treated with cytoreductive nephrectomy and (B) 3014 mRCC patients with 3-mo landmark analysis within the Surveillance, Epidemiology, and End Results (SEER) Research Plus data repository between 2004 and 2017. CI = confidence interval; Ref. = reference; TT = tumor thrombus.

the crucial steps to minimize the risk of perioperative complications in such complex and a priori complicated procedures [21–25].

The current study is not devoid of limitations. First, limitations have to be addressed regarding the sample size and the retrospective design of the current study. Second, selec-

Table 3 – Univariable and multivariable Cox regression models predicting overall mortality of metastatic kidney cancer patients (pT3a vs pT3b vs pT3c) treated with cytoreductive nephrectomy within the Surveillance, Epidemiology, and End Results Research Plus data repository between 2004 and 2017, before and after 6-mo landmark analyses

		Univariable Cox regression			Multivariable Cox regression		
		Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Without 6-mo landmark (n = 3421)	pT3– stage (Ref.: pT3a)	Ref.			Ref.		
	pT3b	0.84	0.70–0.99	0.04	0.94	0.78–1.13	0.49
	pT3c	1.41	1.12–1.76	0.003	1.37	1.09–1.71	0.007
With 6-mo landmark (n = 2629)	pT3–stage (Ref.: pT3a)	Ref.			Ref.		
	pT3b	0.79	0.64–0.98	0.04	0.88	0.71–1.11	0.28
	pT3c	1.37	1.04–1.82	0.03	1.34	1.01–1.77	0.04

CI = confidence interval; Ref = reference; TT = tumor thrombus.

tion biases are clearly applicable and cannot be controlled for, like in previous analyses by Abel et al. [2], as well as Lenis et al. [3]. Within the current study design, which exclusively investigated surgically treated patients, age was restricted to ≤ 75 yr at diagnosis to account for a more pronounced and more heterogeneous perioperative risk profile with increasing age, especially above 75 yr. Third, absence of specific information that would have allowed stratification according to the risk criteria, as well as detailed information regarding systemic therapy, including the sequence of systemic therapy, was not available within the current study population [1,26–35]. Fourth, pT3a-substage patients with tumor features (eg, perinephritic fat invasion) other than vascular invasion were excluded from the initial analyses and were subsequently considered in a secondary analysis without change to the recorded results. Fifth, even though multivariable Cox regression models were adjusted for histological subtypes, sample size limitations did not allow performing specific subgroup analyses within the non-clear cell subgroup of mRCC patients treated with CN [36]. Last but not least, our analyses excluded mRCC patients unexposed to CN due to design considerations, where particular focus was placed in median OS according to tumor thrombus substages without excessive complexity that could have been introduced by considerations, including their pT3-stage counterparts unexposed to CN.

5. Conclusions

Although OM is significantly higher in pT3c mRCC patients than in their pT3b and pT3a counterparts, these individuals may still expect 12 mo or better OS after CN versus virtually 2-yr survival in their pT3a and pT3b counterparts. Nevertheless, a multidisciplinary decision approach must be emphasized for this specific cohort of mRCC patients since perioperative complications are non-negligible within this subgroup of patients.

Author contributions: Benedikt Hoeh 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: Hoeh, Tian, Kosiba, Mandel, Kluth, Chun, Karakiewicz.

Acquisition of data: Flammia, Hohenhorst, Sorce, Saad, Karakiewicz.

Analysis and interpretation of data: Hoeh, Flammia, Hohenhorst, Panunzio, Tappero, Karakiewicz.

Drafting of the manuscript: Hoeh, Flammia, Karakiewicz.

Critical revision of the manuscript for important intellectual content: Gallucci, Briganti, Terrone, Shariat, Graefen, Tilki, Antonelli, Kosiba, Mandel, Kluth, Becker, Chun, Karakiewicz.

Statistical analysis: Hoeh, Flammia, Sorce, Tian.

Obtaining funding: Saad.

Administrative, technical, or material support: Karakiewicz.

Supervision: Saad, Karakiewicz.

Other: None.

Financial disclosures: Benedikt Hoeh 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: Benedikt Hoeh was awarded a scholarship by the Stiftung Giersch.

Funding/Support and role of the sponsor: None.

Data sharing: All data generated for this analysis were from the SEER database. The code for the analyses will be made available upon request.

Ethics statement: All analyses and their reporting followed the SEER reporting guidelines. Owing to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euros.2022.08.011>.

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