

Lessons learned from the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC)

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Abstract Renal cell carcinoma (RCC) extension into the renal vein or the inferior vena cava occurs in 4 %–10 % of all kidney cancer cases. This entity shows a wide range of different clinical and surgical scenarios, making natural history and oncological outcomes variable and poorly characterized. Infrequency and variability make it necessary to share

the experience from different institutions to properly analyze surgical outcomes in this setting. The International Renal Cell Carcinoma–Venous Tumor Thrombus Consortium was created to answer the questions generated by competing results from different retrospective studies in RCC with venous extension on current controversial topics. The aim of this article

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is to summarize the experience gained from the analysis of the world's largest cohort of patients in this unique setting to date.

Keywords Renal cell carcinoma · Inferior vena cava · Tumor thrombus · Radical nephrectomy · Thrombectomy · Multi-institutional · Consortium · Cohort

List of Abbreviations

RCC	renal cell carcinoma
IRCCVTC	international renal cell carcinoma-venous thrombus consortium
IVC	inferior vena cava
CPB	cardiopulmonary bypass
RAE	renal artery embolization
(AJCC)	American Joint Committee on Cancer
(UICC)	Union International Contre le Cancer
SSIGN	Stage, Size, Grade, Necrosis score

Introduction

Renal cell carcinoma (RCC) represents the most lethal urologic malignancy, accounting for 3 % of all cancer deaths. Despite a stage migration toward more localized disease with the routine use of imaging tests in diagnosis, approximately 30 % of RCC patients still present today with locally advanced or metastatic stages of the disease [1, 2]. RCC extension into

the renal vein or the inferior vena cava (IVC), a unique form of locally advanced disease called “tumor thrombus,” occurs in 4 %–10 % of cases [3]. Radical nephrectomy and tumor thrombectomy remains the mainstay of treatment in this particular setting [2]. However, low-frequency presentation rates, coupled with a wide range of different clinical and, thus, surgical scenarios, make natural history and oncological outcomes of this disease very variable and poorly characterized [4].

Under these circumstances, multi-institutional collaborative models may be used for better characterization of the impact of prognostic factors, perioperative complications, and specific disease-profile therapeutic approaches on oncological outcomes [5–7]. In 2006, an international consortium of 11 institutions, established to retrospectively review a combined cohort of 1,215 patients undergoing radical nephrectomy and tumor thrombectomy for RCC throughout the period 1971–2012, was tailored with this purpose (2006–2012), thus giving birth to the International Renal Cell Carcinoma–Venous Thrombus Consortium (IRCC-VTC). Later on in 2012, the IRCC-VTC was expanded to 22 institutions including a total of 2,147 patients from Europe and the U.S. (Table 1). The aim of this article is to summarize the experience gained from the analysis of the world's largest cohort of patients to date in this unique setting. From the beginning, we focused our research on four areas: RCC prognostic factors, surgical issues, perioperative complications, and predictive nomograms.

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RCC Prognostic Factors

Tumor Thrombus Level

Pathologic stage has been shown to be the most important prognostic factor in RCC [8, 9]. However, the impact of tumor thrombus anatomic level on survival rates remains one of the most controversial issues in patients with venous extension, being extensively discussed in the literature [6, 7, 10•, 11–13, 14••, 15–17].

At present, the tumor node metastasis (TNM) staging system remains the most reliable classification system in determining the probability of overall survival (OS) and cancer-specific survival (CSS) rates in these cases. However, this system has lacked a suitable prognostic approach regarding the anatomic level of tumor thrombus inside the venous lumen, and several reports have highlighted the need for a reclassification as significant differences on long-term survival rates had been described for patients with exclusive renal vein involvement or supradiaphragmatic extension [9, 10•, 13, 15]. Therefore, venous involvement limited to the renal vein and supradiaphragmatic extension were finally restaged in

Table 1 The IRCC-VTC: centers and main demographic features (left: patients' characteristics, 2012–now; right: patients' characteristics, 2006–2012)

IRCC-VTC			
		(2012–now)	(2006–2012)
		22 Institutions (Europe & USA)	11 Institutions (Europe & USA)
<i>(n=1,774 (2,147))</i>		<i>(n=1,086 (1,215))</i>	
Age, year (%)			Age, year (%)
≤60	613 (38.0)		≤ 50 456 (42.1)
>60	1,000 (62.0)		51-74 491 (45.0)
			≥ 57 139 (12.9)
Mean (range)	63.3 (19–91)		Median (min.-max.) 62 (25–91)
Sex, <i>N</i> (%)			Sex, <i>N</i> (%)
Female	621 (35.0)		Female 365 (33.6)
Male	1,153 (65.0)		Male 721 (66.4)
TT level (Mayo)			Thrombus level, <i>N</i> (%)
I	400 (38.5)		Renal vein 523 (48.2)
II	318 (30.6)		Level 1 346 (31.9)
III	180 (17.3)		Level 2 143 (13.2)
IV	140 (13.5)		Level 3 74 (6.8)
Fuhrman grade, <i>N</i> (%)			Fuhrman grade, <i>N</i> (%)
1	49 (3.7)		1+2 421 (43.9)
2	437 (33.0)		3 440 (45.8)
3	633 (47.7)		4 99 (10.3)
4	207 (15.6)		
T stage, <i>N</i> (%)			Clinical tumor size, <i>N</i> (%)
T3a	666 (37.8)		<4 cm 64 (6.1)
T3b	869 (43.7)		4–7 cm 260 (24.7)
T3c	228 (13.0)		>7 cm 727 (64.2)
T4	98 (5.6)		
N status, <i>N</i> (%)			N status, <i>N</i> (%)
N0	783 (59.6)		N0 685 (74.2)
N+	273 (20.8)		N+ 238 (25.8)
Nx	257 (19.6)		
Metastasis, <i>N</i> (%)			Metastasis, <i>N</i> (%)
Yes	234 (23.0)		No 821 (75.6)
No	782 (77.0)		Yes 265 (24.4)
Fat invasion, <i>N</i> (%)			Fat invasion, <i>N</i> (%)
Yes	701 (60.9)		No 319 (50.2)
No	450 (39.1)		Yes 316 (49.8)

separated categories (i.e., T3a and T3c, respectively) when, in 2009, the RCC staging system provided by the American Joint Committee on Cancer (AJCC) and the Union International Contre le Cancer (UICC) was updated (Table 2) [9, 14••, 18].

On the basis of the above-mentioned statements, Martínez-Salamanca et al. [14••] attempted to evaluate the accuracy with respect to survival prediction of the updated version of

the TNM classification system in patients with RCC with IVC involvement by investigating the impact of renal vein and different categories of IVC involvement (i.e., pT3b and pT3c) on survival rates. Tumor thrombus level was reported to be an independent predictor of survival in this study (43.2 vs. 37.3 vs. 22.2 months for pT3a, pT3b, and T3c, respectively), thus supporting the use of the revised TNM staging system (Fig. 1a).

Table 2 Updated version of the AJCC/UICC-TNM staging system (7th version, 2009)**T - primary tumor**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension
T2b	Tumors >10 cm limited to the kidney
T3	Tumor extends into major veins or directly invades adrenal gland or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or tumor invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

N - Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node

M - Distant metastasis

M0	No distant metastasis
M1	Distant metastasis

TNM stage grouping

Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0; T1, T2, T3 N1 M0
Stage IV	T4 Any N M0; Any T N2 M0; Any T Any N M1

Metastasis

Presence of metastasis has been reported to be a strong predictor of survival (10.7 % vs. 51.7 % for N0M0 vs. N+/M+, respectively) [10•] in RCC with venous extension, regardless of tumor thrombus anatomic level [6, 19, 20]. The analysis provided by Tosco et al. [21] revealed multiple and nonpulmonary metastases as independent pretreatment prognostic factors, while single-site pulmonary metastasis was shown to be of better prognostic significance when compared with distant metastasis in other sites [22].

A recent analysis from IRCC-VTC on the impact of metastatic spreading on survival [23] confirmed the presence of metastasis at presentation as a significant predictor of survival (52 % vs. 21 % for M0 and M1, respectively) in these patients. Conversely, no significant difference regarding metastasis

location was found. Lymph node spreading or synchronous metastases were not correlated with venous involvement in this study. According to these results, it would be better to base the indication for surgery on the presence of metastases at initial presentation, rather than on their location.

Histological RCC Subtype

Several studies have evaluated the prognostic impact of histological subtype in patients with RCC [24–26]. However, the prognostic significance of this pathologic feature in patients with additional renal vein or IVC involvement has rarely been studied and remains unclear [15, 27–30].

The lack of data on this particular issue favored a recent initiative by Tilki et al. [31••] to evaluate the impact of histologic subtype on survival rates in these particular cases. This study showed that patients with papillary histology had significantly worse outcomes and higher tumor thrombus levels, when compared with patients with other histological subtypes. Five-year CSS rates estimated in this study were 59.5 %, 54.8 %, and 36.8 % for chromophobe, clear-cell, and papillary subtypes, respectively, thus supporting the presence of papillary histology as an independent predictor of cancer-specific death (HR 1.62, CI 1.01–2.61, $p < .05$) with independence of nodal status and presence of distant metastasis (Fig. 1b).

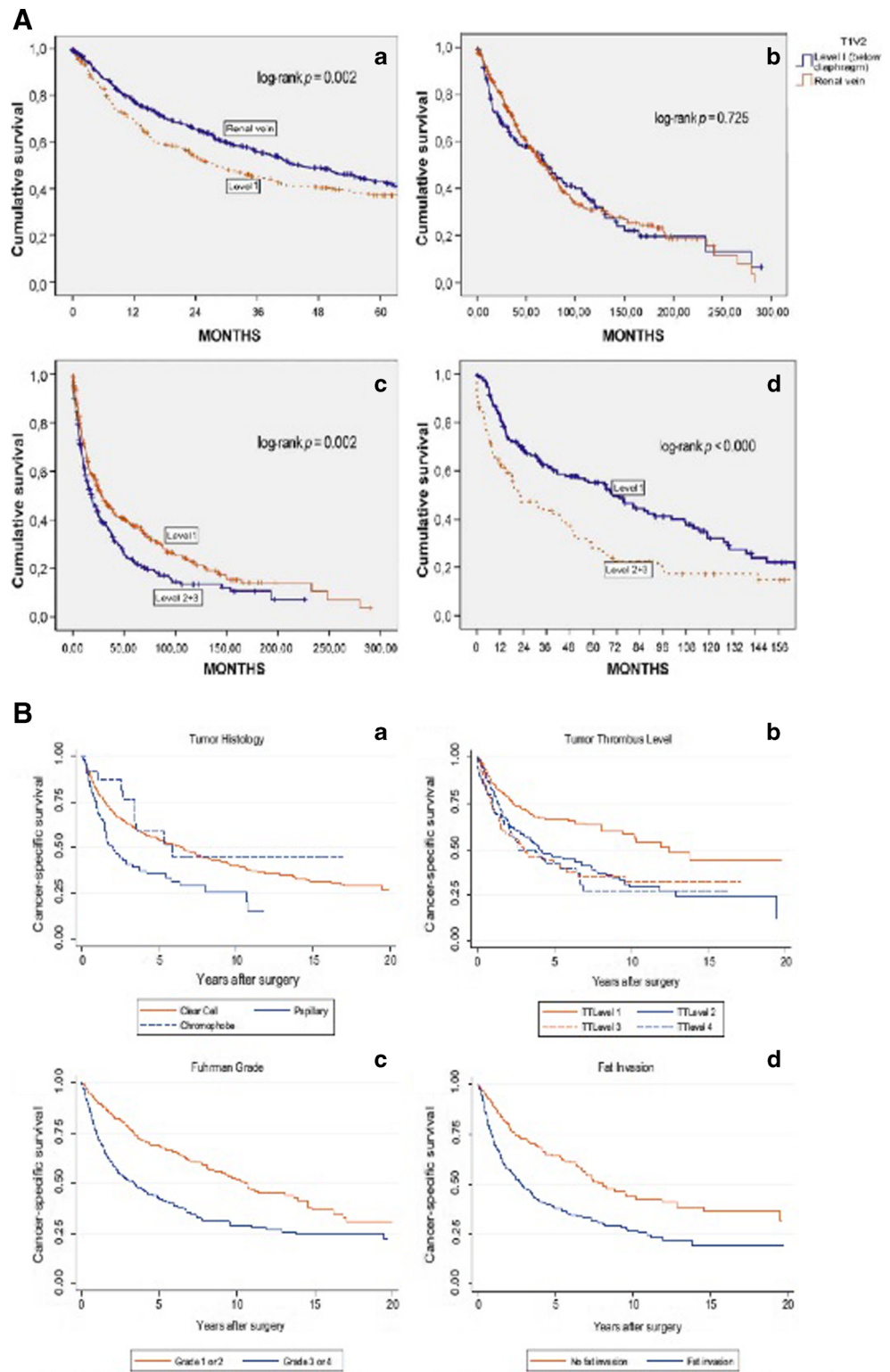
Operative Issues**Presurgical Renal Artery Embolization**

Since its first description with palliative intent in 1973 [32], presurgical renal artery embolization (RAE) has broadened its indications in the last 2 decades, mainly due to steady improvements in imaging, percutaneous approaches, embolic agents, surgical techniques, and perioperative care.

Benefits to be gained by this procedure include decreased operative blood loss, ease of dissection secondary to the development of perirenal tissue edema, decrease in tumor thrombus size favoring less aggressive surgical approaches and morbidity, and overall operative time reduction [6]. However, the frequency (up to 89 %) [33] and the severity of postembolization symptoms have, in many cases, limited the use of this surgical adjunct in many institutions.

On other hand, the effect of RAE on survival rates had been under debate, since different retrospective studies had shown competing outcomes [33, 34]. Therefore, Latal et al. aimed to analyze the impact on perioperative mortality, OS, and CSS in a cohort of 228 patients with RCC and venous extension in whom RAE had been used preoperatively [35]. This study reported no additional benefit in OS or CSS for patients receiving RAE, and no significant difference in perioperative

Fig. 1 Kaplan-Meier cancer-specific survival (CSS) **a** According to pT3a/pT3b/pT3c. **b** According to histologic subtype, tumor thrombus level, Fuhrman grade, and fat invasion



mortality was noted. However, an important issue regarding the time interval from RAE to surgery could not be conveniently raised due to the variability of the temporary margins observed among the patients included in the cohort (0–6 weeks).

The IRCC-VTC has studied the impact of RAE on perioperative mortality and OS/CSS [36]. We analyzed a total of 1,042 patients, 228 (77 %) with and 728 (23 %) without RAE. Perioperative mortality was similar between the two groups (4 %). RAEs were performed on the basis of level of

thrombus: level I (15 %), level II (29 %), level III (28 %), and level IV (60 %). Five-year OS and CSS were 39 % (33–47) and 49 % (42–56), respectively, for RAE patients and 36 % (32–40) and 48 % (43–51) for non-RAE patients (OS $p=.21$ and CSS $p=.43$).

In conclusion, on the basis of the IRCC-VTC experience, patients with/without preoperative RAE showed similar OS, CSS, and perioperative mortality rates [36].

Presurgical RAE used as an adjuvant procedure for patients requiring nephrectomy and tumor thrombectomy may have operative advantages. However, preoperative RAE acute toxicity may delay surgical intervention in patients with poor performance status. In addition, time interval between the RAE and nephrectomy may impact survival rates. Therefore, it is difficult to draw reliable conclusions about the role of preoperative RAE in the management of patients with RCC and venous involvement.

Cardiopulmonary Bypass

Supradiaphragmatic and intraatrial tumor thrombi pose a challenge for the treating surgeon given the operative difficulty and the possibility for potential intraoperative complications, including massive blood loss and pulmonary embolism [11, 36–38].

Cardiopulmonary bypass (CPB) is used as a surgical adjunct in RCC invading the IVC to provide continuous cardiac venous return, thus preserving cardiovascular output when the IVC is cross-clamped for thrombus withdrawal. The use of CPB meant a technical revolution in radical nephrectomy and tumor thrombectomy, since up to its emergence in the mid-1960s, the rate of intra- and postoperative complications in the excision of suprahepatic and supradiaphragmatic tumor thrombi was extremely high. Conversely, the utilization of this surgical system has recently been associated with morbidity rates that cannot be overstated, including haematological, hepatic, renal, neurological, and septic, among others [36, 39, 40]. This set of potential surgical sequelae has favored the development of procedures with the intention of avoiding the use of sternotomy and CPB (i.e., liver transplantation techniques) [41] or to permit a decrease in the number and severity of CPB-related complications (i.e., minimally invasive thoracotomy, “beating-heart” techniques, antegrade cerebral perfusion, and mild hypothermia) in this particular setting [42].

Despite the theoretical benefits associated with the reduction in CPB-related morbidity, the impact of this surgical adjunct on RCC with venous involvement survival rates had remained unclear since the first reports on this subject. Thus, the IRCC-VTC aimed to evaluate the effect of CPB on cancer-specific mortality, in a large cohort of 271 patients with tumor thrombus levels III and IV. Mean follow-up in this study was 39.8 (0–258) months, with a median survival of 30 months.

The 5-year cancer-specific mortality rates observed were 31 % (level III with CPB), 31 % (level III without CPB), and 28 % (level IV with CPB). Level IV without CPB group did not reach the minimum time period to calculate. These findings support the conclusion that from the oncological outcomes perspective, both approaches (i.e., with or without the use of CPB) are safe for the treatment of RCC with level III and IV tumor thrombus [44].

Perioperative Complications

Radical nephrectomy and tumor thrombectomy have been shown to be associated with major perioperative morbidity (up to 70 %) and mortality (3 %–16 %) in several retrospective series [16, 36, 43, 44]. A number of factors influencing perioperative mortality have been also identified, including patient comorbid conditions, performance status [45], distant metastatic spreading, and tumor thrombus extension above the diaphragm [20]. Although perioperative morbidity (i.e., complication rate) according to the anatomic level of tumor thrombus has been studied [6], no correlation between preoperative mortality and cephalad extent of the thrombus has been reported up to the present.

The IRCC-VTC evaluated the association between tumor thrombus level according to the Mayo Clinic classification system [43] and perioperative complications observed after the procedure. Thereafter, both variables were correlated with perioperative mortality [46]. Postoperative complications were recorded for a 30-days period and graded according to the Clavien–Dindo postoperative complication grading system [47–50]. Postoperative complications were observed in 183 patients (34 %), which in 69 patients (13 %) were recorded as high grade (grades 3–5). The overall 30-day mortality rate was 1.8 %. Level of tumor thrombus according to the Mayo Clinic classification system was shown to be an independent predictor of complications (pooled $p=.001$), and high-grade complications (pooled $p=.029$) [51].

Predictive Nomograms for Cancer-Specific Survival

Surgical treatment outcomes in patients with RCC depend on multiple factors. Various clinical and pathological features have been shown to influence prognosis. Different attempts to create models in order to stratify the risk of recurrence and predict survival in these patients have been conducted.

Nomograms derived from large multi-institutional series, integrating all independent prognostic variables that influence a particular oncological setting, have been shown to be more accurate than the TNM staging system for predicting outcomes following treatment. These predictive models combine

numerous clinical features to provide a better prediction of survival and recurrence.

The predictive nomogram proposed by Kattan et al. [52] and the stage, size, grade, and necrosis (SSIGN) score from the Mayo Clinic [53, 54] were the first initiatives in the field of RCC. These tables include different factors significantly involved in the risk of recurrence following nephrectomy for localized RCC. Anatomic tumor extent, histologic tumor subtype and grade, evidence of intratumoral necrosis, presence of clinical symptoms, performance status, and laboratory test parameters were included in these analyses. Models were prospectively validated showing accuracy prediction rates varying from 78 % to 87 % [55–57].

Locally advanced RCC presents multiple clinical scenarios involving a wide range of prognostic situations. Appropriate treatment selection and timely follow-up depend mainly on accurate prediction of survival and disease recurrence. Therefore, the experience gained from the initial attempts in localized RCC gave rise to prognostic tables to be used in the locally advanced setting [52, 53]. Likewise, a predictive model for assessing CSS has been designed and conducted recently using the surgical experience provided by the IRCC-VTC data set [58]. This model was based initially on previously confirmed postoperative prognostic variables, including age, gender, presurgical RAE, nodal status, presence of metastasis, tumor thrombus level, pathologic fat invasion and primary tumor size, stage, and grade. Visible metastasis at the time of surgery (HR 2.5, $p < .001$), tumor size (HR 1.1, $p < .001$), and presence of pathologic fat invasion (HR 2.1 $p < .001$) achieved the independent predictor status to be included in the multivariate analysis. Thereafter, the nomogram was internally validated with a 200-repetition bootstrap analysis. The internal-bootstrapped concordance index was 0.69. This three-variable-based nomogram may be used to predict accurately the probability of 5-year CSS in RCC patients involving the renal vein or the IVC following surgical treatment. In addition, this predictive table may be useful in counseling patients considering surgery for RCC and venous extension.

Conclusions

Involvement of the renal vein or the IVC by tumor is relatively infrequent, accounting for 4 %–10 % of all RCC cases. This unique form of locally advanced RCC presents a wide range of clinical scenarios and different prognostic situations, for which specific surgical approaches have been described. Despite the great clinical and technical variability, complete removal of neoplastic tissue remains the mainstay of treatment in all these cases.

Infrequency and variability make it necessary to share the experience from different institutions to properly analyze surgical outcomes in this setting. IRCC-VTC was created to

answer the questions generated by competing results from different retrospective studies in RCC with venous extension on current controversial topics.

On the basis of the analysis of a clinical, surgical, and pathological data set from the world's largest cohort of patients with RCC and venous involvement to date, several issues concerning prognostic factors, operative procedures, and surgical outcomes in this setting have been addressed. Lessons learned from the IRCC-VTC include the recognition of tumor thrombus anatomic level as an independent survival predictive factor, the confirmation of radical surgery as the mainstay of treatment for these patients even in the metastatic setting, the identification of papillary histological subtype as a magnifier of the oncological risk when compared with other pathological subtypes, and the description of a direct relationship between the tumor thrombus level and the number and severity of complications, making thrombus level according to the Mayo Clinic classification system a strong predictor of perioperative complications in patients with RCC and venous extension.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Juan I. Martínez-Salamanca, Dr. Estefania Linares, Dr. Javier González, Dr. Roberto Bertini, Dr. Joaquín A. Carballido, Dr. Thomas Chromecki, Dr. Sia Daneshmand, Dr. Christopher P. Evans, Dr. Paolo Gontero, Dr. Axel Haferkamp, Dr. Markus Hohenfellner, Dr. William C. Huang, Dr. Theresa M. Koppie, Dr. Viraj A. Master, Dr. Rayan Matloob, Dr. James M. McKiernan, Dr. Carrie M. Mlynarczyk, Dr. Francesco Montorsi, Dr. Hao G. Nguyen, Dr. Giacomo Novara, Dr. Sascha Pahernik, Dr. Juan Palou, Dr. Raj S. Pruthi, Dr. Krishna Ramaswamy, Dr. Oscar Rodriguez Faba, Dr. Paul Russo, Dr. Shahrokh F. Shariat, Dr. Martin Spahn, Dr. Carlo Terrone, Dr. Derya Tilki, Dr. Daniel Verghe, Dr. Eric M. Wallen, Dr. Evangelos Xylinas, Dr. Richard Zigeuner, and Dr. John A. Libertino each declare no potential conflicts of interest relevant to this article.

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- Of importance
- Of major importance

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