# Impact of Synchronous Metastasis Distribution on Cancer Specific Survival in Renal Cell Carcinoma after Radical Nephrectomy with Tumor Thrombectomy

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**Abbreviations and Acronyms**

CN = cytoreductive nephrectomy

CSS = cancer specific survival

IVC = inferior vena cava

mRCC = metastatic renal cell cancer

RCC = renal cell cancer

TT = tumor thrombus

**Purpose:** Metastatic renal cell carcinoma can be clinically diverse in terms of the pattern of metastatic disease and response to treatment. We studied the impact of metastasis and location on cancer specific survival.

**Materials and Methods:** The records of 2,017 patients with renal cell cancer and tumor thrombus who underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 centers in the United States and Europe were analyzed. Number and location of synchronous metastases were compared with respect to patient cancer specific survival. Multivariable Cox regression models were used to quantify the impact of covariates.

**Results:** Lymph node metastasis (155) or distant metastasis (725) was present in 880 (44%) patients. Of the patients with distant disease 385 (53%) had an

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isolated metastasis. The 5-year cancer specific survival was 51.3% (95% CI 48.6–53.9) for the entire group. On univariable analysis patients with isolated lymph node metastasis had a significantly worse cancer specific survival than those with a solitary distant metastasis. The location of distant metastasis did not have any significant effect on cancer specific survival. On multivariable analysis the presence of lymph node metastasis, isolated distant metastasis and multiple distant metastases were independently associated with cancer specific survival. Moreover higher tumor thrombus level, papillary histology and the use of postoperative systemic therapy were independently associated with worse cancer specific survival.

**Conclusions:** In our multi-institutional series of patients with renal cell cancer who underwent radical nephrectomy and tumor thrombectomy, almost half of the patients had synchronous lymph node or distant organ metastasis. Survival was superior in patients with solitary distant metastasis compared to isolated lymph node disease.

**Key Words:** carcinoma, renal cell; neoplasm metastasis; survival; prognosis; vena cava, inferior

Patients with advanced stage renal cell carcinoma are at higher risk for a locally aggressive primary tumor which can include a thrombus extending into the renal vein, vena cava or right atrium.[1] In patients with metastatic RCC and a tumor thrombus, extirpation can palliate symptoms, and eliminate the risk of thrombus propagation and its associated morbidities. In the era of targeted therapy it is possible that cytoreductive nephrectomy with tumor thrombectomy can improve survival. However, the degree of oncologic benefit that may derive from CN is not always clear. This is, in part, due to the diversity of mRCC in terms of the pattern of metastases, timing of progression, spectrum of patient health and response to systemic therapy. Current survival prediction in mRCC relies on clinical factors such as performance status, laboratory studies (serum albumin, lactate dehydrogenase, calcium), T stage, N stage and symptoms from metastasis.[2–4] The number and location of metastases have been thought to impact survival after CN as they may represent markers of tumor aggressiveness and biology. Evidence of their predictive ability has been mixed.[5–8] In this study we investigated how the pattern of metastatic spread impacts CSS in patients undergoing radical nephrectomy with tumor thrombectomy. Therefore, we used data from an international cohort of patients with RCC and TT.

## PATIENTS AND METHODS

### Patient Selection and Data Collection

For this institutional review board approved study all participating sites provided the necessary institutional data sharing agreements before initiation of the study. A total of 22 United States and European centers provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis the database was frozen and the final data set was produced for the current analysis. The records of 2,017 patients with RCC and venous thrombus who underwent radical nephrectomy and complete tumor thrombectomy between 1971 and 2012 were reviewed.

### Pathological Evaluation and Macroscopic Vascular Involvement

All surgical specimens were processed according to standard pathological procedures. Tumor size was evaluated on fixed pathological specimens. Histological subtype was determined according to the 1997 WHO Heidelberg classification.[9] Tumor nuclear grade was determined according to the Fuhrman system. Pathological staging was designated according to the 2009 TNM classification of the American Joint Committee on Cancer.[10]

### Tumor Thrombus Level

The Mayo classification was used for the macroscopic vascular involvement.[11] Level I—TT is at the entry of the renal vein or within the inferior vena cava less than 2 cm from the confluence of the renal vein and the IVC. Level II—thrombus extends within the IVC more than 2 cm above the confluence of the renal vein and IVC but still remains below the hepatic veins. Level III—thrombus involves the intrahepatic IVC. The size of the thrombus ranges from a narrow tail that extends into the IVC to one that fills the lumen and enlarges the IVC. Level IV—thrombus extends above the diaphragm or into the right atrium.

### Followup

Followup was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3 months for the first year, semiannually for the second year and annually thereafter. Followup visits consisted of a physical examination and serum chemistry evaluation, including liver function tests and alkaline phosphatase. Diagnostic imaging (eg ultrasonography, computerized tomography of the abdomen/pelvis with intravenous contrast) and chest radiography were performed twice yearly and at the discretion of the treating physician when clinically indicated. When patients died the cause of death was determined by the treating

physicians, by chart review corroborated by death certificates or by death certificates alone. Patients who were identified as having died of RCC had progressive, widely disseminated and often highly symptomatic metastases at the time of death. Perioperative mortality (death within 30 days of surgery) was censored at time of death for cancer specific survival analyses.

### Statistical Analysis

The Kaplan-Meier method was used to calculate survival functions (CSS) and differences were assessed with the log rank statistic. Univariable and multivariable survival analyses were performed using the Cox proportional hazards regression model. In all models proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual based test. The p values were calculated with t-tests, chi-square tests, Kruskal-Wallis tests and ordered logistic regression. All reported p values are 2-sided, and statistical significance was set at $p < 0.05$. No adjustments were made for multiple statistical tests. Data were analyzed using Stata® 11 for Windows®.

## RESULTS

### Clinical and Pathological Characteristics

A total of 2,017 patients with RCC and venous thrombus underwent radical nephrectomy and tumor thrombectomy. Mean age for the entire group was 63.2 years (range 19 to 91). Of the 2,017 patients 880 (43.6%) had synchronous metastases. Distant metastases were present in 725 (35.9%) patients, of whom 385 (53.1%) had a solitary metastasis (defined as a single lesion in a single organ) and 340 (46.9%) had multiple distant metastases. There were 155 patients with an isolated lymph node metastasis. The clinical and pathological features of these patients are compared in the supplementary table (http://jurology.com/). The distribution of sites of solitary metastases is summarized in table 1. Postoperative systemic therapy was administered at investigator discretion to 6.0% of patients, all of whom had metastatic disease.

### Clinical Outcomes and Association of Presence and Location of Metastases with Survival

Median followup was 82.3 months for patients alive at last followup (IQR 34.1–158.5). Overall 1,172 patients (58.1%) were deceased at the time of analysis, including 828 (41.1%) who died of RCC.

**Table 1.** *Distribution of solitary metastases*

| | % |
|---|---|
| Brain | 7.8 |
| Lung | 48.4 |
| Liver | 12.1 |
| Bone | 10.3 |
| Other | 21.4 |

The 5-year CSS was 51.3% (95% CI 48.6–54.1) in the entire patient group.

The 5-year CSS estimates in patients without metastases, with solitary distant metastasis and with multiple distant metastases were 71.3% (95% CI 67.8–74.5), 36.8% (95% CI 27.0–46.5) and 20.8% (95% CI 15.8–26.3), respectively. Patients with an isolated lymph node metastasis had a 5-year CSS estimate of 17.3% (95% CI 9.3–27.4).

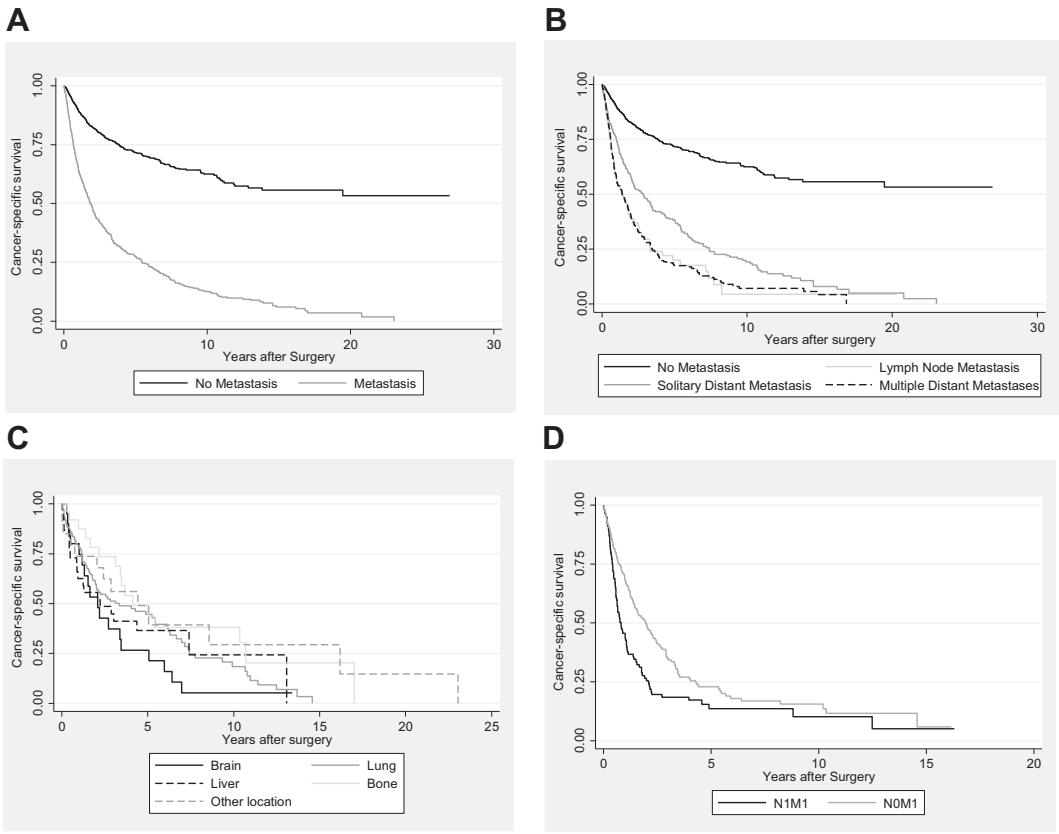
On univariable analysis the presence of metastases was associated with significantly shorter CSS (part *A* of figure). Compared with patients with a solitary distant metastasis at surgery, patients with multiple distant metastases had a shorter CSS (part *B* of figure). Patients with isolated lymph node metastases had a significantly worse CSS compared to those with a solitary distant metastasis (part *B* of figure). The location of distant metastases did not have any significant effect on survival (part *C* of figure). Patients with distant metastasis without lymph node metastasis (N0M1) had a significantly better CSS than patients with M1 disease who had lymph node metastasis (N1M1) (part *D* of figure).

On multivariable analysis the presence of distant metastasis was independently associated with CSS (solitary metastasis HR 1.83, CI 1.31–2.56, $p < 0.001$; multiple metastases HR 2.29, CI 1.57–3.32, $p < 0.001$, table 2). Moreover higher tumor thrombus level, papillary histology and postoperative systemic therapy were independently associated with worse CSS, while initial tumor size had no impact on survival. The period of treatment did not have an effect on outcomes.

## DISCUSSION

Among patients with distant metastases we found improved survival after radical nephrectomy with tumor thrombectomy in those with a solitary metastasis vs multiple metastases. The positive impact of oligometastatic disease on survival in mRCC has been demonstrated in multiple retrospective studies. However, these studies may not necessarily reflect survival after radical nephrectomy given the inclusion of patients who did not undergo nephrectomy and those with metachronous disease. The SWOG 8949 randomized controlled trial of interferon alpha-2b, with or without CN, demonstrated that patients without measurable distant disease experienced significantly improved survival after radical nephrectomy than those with measurable disease.[12] Additionally, Leibovich et al collectively examined the survival of 900 patients with mRCC and found that multiple metastases were predictive of worse CSS.[7,13]

Despite these studies, there is ample evidence arguing against the positive prognostic impact of




Probability estimates of CSS in patients with RCC and tumor thrombus stratified by presence of metastasis ($p < 0.001$) (*A*), type of metastasis ($p < 0.001$) (*B*), location of metastasis ($p = 0.14$) (*C*) and node metastasis status ($p < 0.001$) (*D*).

oligometastatic disease after CN. The findings of the SWOG study must be taken in the context of the analysis that combined data with the EORTC (European Organisation for Research and Treatment of Cancer) 30947 randomized trial given their identical protocols.[14] The pooled analysis did not demonstrate that the degree of disease measurability independently impacted survival.[5] Margulis et al examined the records of more than 600 patients who underwent CN, and developed preoperative and postoperative nomograms to predict survival.[3] They did not find that the number of metastases was associated with survival. Lastly, Vasselli et al analyzed the survival of 154 patients after CN before interleukin-2 therapy, and did not find an association between survival and the number of organs with metastases.[15]

There are several explanations for the differences in CSS associated with distant disease burden seen in this study. It is possible that immune suppression caused by the primary tumor, a putative mechanism for the oncologic benefit of CN, may have more attenuated effects in those with a large volume of distant disease. It is also possible that the findings are a function of studying only patients with a TT, which may represent a subset of RCC with unique biological behavior. For example, it could be hypothesized that these tumors, having already shown a propensity for vascular invasion, have a greater ability to seed hematogenous metastases. Therefore, CN with tumor thrombectomy in patients with oligometastatic disease could lead to more prolonged disease latency.

Certain metastasis locations such as brain, liver and bone have been shown to negatively impact survival in mRCC.[8,16,17] The impact of these sites of metastasis on survival after CN is unclear. Leibovich et al found that bone and lung metastases had better survival compared to other organs when reviewing records from 173 patients after CN and immunotherapy.[13] Culp et al reviewed the records of 566 patients and found that liver metastases were independently predictive of worse survival.[4] However, a recent followup study by Margulis et al did not show the location of metastasis to be significant.[3] This finding corresponds with the pooled analysis of the randomized controlled trials of CN which did not show that the location of metastasis (lung only vs not lung only) was prognostic for survival.[5] We examined survival

**Table 2.** *Univariable and multivariable Cox regression analysis assessing prognostic factors associated with CSS*

| | Univariable Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| Covariate | HR | 95% CI | p Value | HR | 95% CI | p Value |
| Age | 0.99 | 0.99 — 1.00 | <0.05 | 1.00 | 0.99 — 1.01 | 0.89 |
| Yr of surgery: | | | | | | |
| 1971 — 1984 | 1.10 | 0.79 — 1.53 | 0.57 | 1.32 | 0.86 — 2.03 | 0.21 |
| 1985 — 1998 | 1.18 | 1.01 — 1.37 | <0.05 | 1.24 | 0.93 — 1.66 | 0.14 |
| 1999 — 2012 | Ref | | | | | |
| TT level (Mayo): | | | | | | |
| I | Ref | | | | | |
| II | 1.81 | 1.42 — 2.30 | <0.001 | 1.48 | 1.11 — 1.97 | <0.01 |
| III | 2.09 | 1.58 — 2.76 | <0.001 | 1.60 | 1.13 — 2.26 | <0.01 |
| IV | 2.22 | 1.65 — 2.98 | <0.001 | 1.52 | 0.99 — 2.34 | 0.05 |
| Histology: | | | | | | |
| Clear cell | Ref | | | | | |
| Papillary | 1.81 | 1.43 — 2.29 | <0.001 | 1.61 | 1.09 — 2.37 | <0.05 |
| Chromophobe | 0.66 | 0.33 — 1.31 | 0.23 | 1.38 | 0.62 — 3.09 | 0.43 |
| Other | 1.85 | 1.37 — 2.51 | <0.001 | 2.01 | 1.39 — 2.89 | <0.001 |
| Adjuvant therapy | 2.26 | 1.80 — 2.83 | <0.001 | 1.61 | 1.13 — 2.28 | <0.01 |
| Tumor size (cm): | | | | | | |
| Less than 4 | Ref | | | | | |
| 4—7 | 1.60 | 1.05 — 2.43 | <0.05 | 1.27 | 0.73 — 2.22 | 0.39 |
| Greater than 7 | 2.73 | 1.83 — 4.09 | <0.001 | 1.25 | 0.73 — 2.13 | 0.42 |
| Nx/N0 | Ref | | | | | |
| N+ | 3.25 | 2.69 — 3.93 | <0.001 | 2.14 | 1.52 — 3.00 | <0.001 |
| M0 | Ref | | | | | |
| Solitary distant metastasis | 2.70 | 2.29 — 3.17 | <0.001 | 1.83 | 1.31 — 2.56 | <0.001 |
| Multiple distant metastases | 4.12 | 3.47 — 4.89 | <0.001 | 2.29 | 1.57 — 3.32 | <0.001 |

stratified by the individual organ metastases and did not find any significant difference in survival. Interestingly, patients with brain only disease trended toward worse survival. However, this trend may not necessarily reflect the changes in treating brain metastases where stereotactic radiosurgery has shown promise, especially in patients with a solitary metastasis.[18,19]

We found regional lymph node metastasis portends a particularly poor prognosis after radical nephrectomy with tumor thrombectomy. In fact, patients with isolated lymph node disease had worse CSS compared with patients with a single distant metastasis. There was no significant difference in survival between patients with multiple distant metastases and lymph node metastasis. Series have consistently shown better survival in stage III RCC compared with stage IV disease.[2,20] The profound negative impact of positive lymph nodes on survival, especially in those treated surgically, has also been described. In fact, 2 studies have shown that lymph node involvement is more predictive of survival than the number of distant metastases after CN.[3,15]

Pantuck et al reviewed records from 900 patients with advanced RCC treated surgically and found that patients with pathological N0M1 disease had overall survival similar to those with N1M0 disease.[21] Furthermore, they found that patients with positive lymph nodes who underwent lymphadenectomy had improved survival and a trend toward improved response to immunotherapy. Placed in this context, our finding of worse survival in pathological node positive disease, all of whom received a lymphadenectomy, is interesting and potentially attributable to differences in tumor biology in patients with a TT such as differences in the risk of hematogenous metastasis. Our analysis reinforces 2 important points in patients with RCC with TT. 1) Despite the risk of hematogenous micrometastasis in all of these patients, those without metastatic disease have significantly improved survival after surgery compared to mRCC with TT. 2) We demonstrated that patients with mRCC with TT can experience a durable response after CN. Even in those with multiple distant metastases, 5-year CSS was 20.8%. Choueiri et al confirmed that CN can remain a viable treatment in patients with multiple metastases, examining survival in 314 patients treated with targeted therapy.[22] In a subset analysis, patients with more than 1 site of metastatic disease who underwent CN had a significantly improved overall survival compared with those who did not have surgery (20.2 vs 8.5 months).

This study has several strengths that warrant mention. By using an international, multi-institutional database, the findings may be a better reflection of real-world practice and, therefore, may be more generalizable. Our study includes patients with nonclear cell histology, which has recently been shown to impact survival in patients

with a TT undergoing surgery.[23] CN has been shown to be efficacious in patients with nonclear cell histology.[24] Additionally, radical nephrectomy with tumor thrombectomy represents a formidable surgical challenge with significant morbidity.[25] Therefore, examining survival exclusively in this population may yield outcomes not necessarily seen in all patients who undergo radical nephrectomy.

Although to our knowledge the present study involves the largest collection of patients with RCC and TT to date, the findings must be interpreted with caution. Retrospectively analyzing patients who underwent surgery introduces a selection bias and makes it difficult to draw conclusions regarding the decision to pursue a CN. Conti et al published a retrospective analysis with propensity scoring to help answer this question, finding CN to be associated with improved survival compared with no surgery.[26] More definitive conclusions on the efficacy of CN with targeted therapy may need to wait for the results of CARMENA (Clinical Trial to Assess the Importance of Nephrectomy).[26] Furthermore, only a small portion of the patients received systemic therapy and we do not have detailed information on type of systemic therapy. Our data span 41 years, and during this time medical and surgical treatment for advanced RCC changed dramatically. However, two-thirds of the patients were treated from 1999 to 2012 and period of treatment did not have an independent effect on outcomes. Despite the limitations, this study provides valuable observational information in describing how the distribution and number of metastases impacts CSS after radical nephrectomy and tumor thrombectomy.

## CONCLUSIONS

In our international cohort almost half of patients undergoing radical nephrectomy and tumor thrombectomy had synchronous lymph node or distant metastasis. Among these patients a significant subset achieved a durable response after surgery. In mRCC after CN, survival was improved in those with isolated, distant metastasis compared to multiple distant metastases and those with lymph node metastasis. The organ of metastasis was not associated with CSS. These findings can help with patient counseling and potentially identify those who require more aggressive adjuvant therapy.

## REFERENCES


1. Pantuck AJ, Zisman A, Dorey F et al: Renal cell carcinoma with retroperitoneal lymph nodes. Impact on survival and benefits of immunotherapy. Cancer 2003; **97:** 2995.
2. Motzer RJ, Mazumdar M, Bacik J et al: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999; **17:** 2530.
3. Margulis V, Shariat SF, Rapoport Y et al: Development of accurate models for individualized prediction of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Eur Urol 2013; **63:** 947.
4. Culp SH, Tannir NM, Abel EJ et al: Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 2010; **116:** 3378.
5. Flanigan RC, Mickisch G, Sylvester R et al: Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004; **171:** 1071.
6. Negrier 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 2002; **13:** 1460.
7. Leibovich BC, Cheville JC, Lohse CM et al: A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. J Urol 2005; **174:** 1759.
8. Han KR, Pantuck AJ, Bui MH et al: Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. Urology 2003; **61:** 314.
9. Störkel S, Eble JN, Adlakha K et al: Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997; **80:** 987.
10. Edge SB and Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; **17:** 1471.
11. Neves RJ and Zincke H: Surgical treatment of renal cancer with vena cava extension. Br J Urol 1987; **59:** 390.
12. Flanigan RC, Salmon SE, Blumenstein BA et al: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001; **345:** 1655.
13. Leibovich BC, Han KR, Bui MH et al: Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003; **98:** 2566.
14. Mickisch GH, Garin A, van Poppel H et al: Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001; **358:** 966.
15. Vasselli JR, Yang JC, Linehan WM et al: Lack of retroperitoneal lymphadenopathy predicts survival of patients with metastatic renal cell carcinoma. J Urol 2001; **166:** 68.
16. 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 2014; **65:** 577.
17. Wronski M, Maor MH, Davis BJ et al: External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M.D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 1997; **37:** 753.
18. Marko NF, Angelov L, Toms SA et al: Stereotactic radiosurgery as single-modality treatment of incidentally identified renal cell carcinoma brain metastases. World Neurosurg 2010; **73:** 186.
19. Vickers MM, Al-Harbi H, Choueiri TK et al: Prognostic factors of survival for patients with metastatic renal cell carcinoma with brain metastases treated with targeted therapy: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Clin Genitourin Cancer 2013; **11:** 311.

20. Karakiewicz PI, Trinh QD, Bhojani N et al: Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. Eur Urol 2007; **51:** 1616.

21. Pantuck AJ, Zisman A, Dorey F et al: Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol 2003; **169:** 2076.

22. Choueiri TK, Xie W, Kollmannsberger C et al: The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 2011; **185:** 60.

23. Tilki D, Nguyen HG, Dall'Era MA et al: Impact of histologic subtype on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus. Eur Urol 2014; **66:** 577.

24. Aizer AA, Urun Y, McKay RR et al: Cytoreductive nephrectomy in patients with metastatic non-clear-cell renal cell carcinoma (RCC). BJU Int 2014; **113:** E67.

25. Abel EJ, Thompson RH, Margulis V et al: Perioperative outcomes following surgical resection of renal cell carcinoma with inferior vena cava thrombus extending above the hepatic veins: a contemporary multicenter experience. Eur Urol 2014; **66:** 584.

26. Conti SL, Thomas IC, Hagedorn JC et al: Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. Int J Cancer 2014; **134:** 2245.