Commentary

Comprehensive characterization of the perioperative morbidity of cytoreductive nephrectomy

Andrew Leone, Gregory Diorio, Kamran Zargar-Shoshtari, Philippe E. Spiess

Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

Correspondence to: Philippe E. Spiess, MD, MS, FRCS(C). Associate Member, Department of GU Oncology, Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33618, USA. Email: philippe.spiess@moffitt.org.

Submitted Mar 14, 2016. Accepted for publication Mar 24, 2016.
doi: 10.21037/tau.2016.03.21
View this article at: http://dx.doi.org/10.21037/tau.2016.03.21

The authors report a single institution retrospective analysis of the reported complications and delay to initiation of systemic therapy in a cohort of 294 patients with metastatic renal cell carcinoma (1). This is the largest series evaluating this novel study question. There is presently no randomized controlled data in the era of targeted therapy demonstrating a survival benefit of upfront cytoreductive nephrectomy (CN). Despite this, CN is commonly utilized in well selected patients utilizing extrapolated data from the immunotherapy era. There is some evidence from the National Cancer Database, that adoption of CN from 2005–2008 (era of targeted therapy) actually has been decreasing with improvement in the effectiveness and enhanced reported toxicity profile of targeted therapy (2). Questions remain regarding which patients derive optimal benefit from CN.

The morbidity associated with upfront CN (previously reported as high as 37% with mortality as high as 6.6%) and may delay administration of targeted therapies (3). In the era of targeted therapy, evidence from NCDB analysis suggests that patients are increasing receiving systemic therapy after CN, however, less than 50% of eligible patients will receive systemic therapy (4).

There are currently two ongoing randomized trials examining CN with targeted therapies, CARMENA (NCT0093033) and SURTIME [NCT01099423 (5)]. Unfortunately, CARMENA, which randomized patients to CN + sunitinib *vs.* sunitinib alone will not be completed until 2018 and is limited by non-inferiority design and patient accrual issues. With the development of multiple targeted agents the study design will likely be obsolete by completion. The SURTIME trial aims to assess timing of CN relative to treatment with sunitinib. Both trials only include patients with high performance status (ECOG 0/1) patients and only clear cell type is included.

The authors of this study aimed to determine the effect of CN on administration of systemic therapy. They conclude found that only 11% of the cases who experienced a delay to systemic therapy greater than 60 days were secondary to surgical complications in patients who experienced delay to CN more than 60 days, only 11% of the cases were secondary to surgical complications whereas previous studies have suggested a higher rate of 19% (1,6). Factors in this study associated with perioperative complications were presence of liver metastases, intraoperative transfusion, and node positive disease. There are some limitations to the study. First, patients were excluded in the systemic therapy analysis if their medical oncologist did not treat with targeted therapy because of opting for surveillance. This raises the question of whether these patients were excluded for reasons related to ensuing postoperative complications. Second, there is an inherent selection bias in the patient population who underwent CN. Patient selection is critically important in deciding on treatment approach including implementation of CN and targeted therapy. Previous studies identified clinical/demographic factors associated with lack of survival benefit for CN. In patients with more than four negative prognostic factors: serum albumin below normal, lactate dehydrogenase above normal, clinical tumor stage of T3 or greater, presence of liver metastasis, symptoms at presentation resulting from a metastatic site, retroperitoneal lymphadenopathy, and supradiaphragmatic lymphadenopathy did not achieve a benefit from CN (7). Finally, the parameters included in the multivariate analysis are not robust and stage, a critical factor was excluded from one of models raising into

question its true clinical validity.

The largest study to date investigating the role of CN in metastatic RCC (mRCC) patients was published in 2014 (8). The study compared 982 patients who underwent CN to 676 patients who did not. CN was found to be of benefit in patients with less than four International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors: hemoglobin below lower limit of normal (LLN), corrected calcium greater than upper limit of normal (ULN), neutrophils above ULN, platelets greater than ULN, Karnofsky performance status <80%, and time from diagnosis to treatment <1 year. These studies suggest that many factors are necessary to consider in identifying patients garnering benefit from CN. Based on the confluence of patient clinical and demographic parameters, once patients are deemed appropriate candidates for CN questions remain regarding timing of CN.

Because of toxicity of immunotherapy, CN was traditionally performed prior to receiving systemic therapy. In this series, all patients received CN then targeted therapy. However, with a lower adverse effect burden, questions remain whether targeted therapy should be administered prior to CN. In an effort to reduce primary tumor size and therefore decrease associated perioperative morbidity, Abel *et al*. 2011 explored 168 patients treated with targeted agents prior to CN (9). The authors concluded that primary tumor response with 60 days after initiation of systemic therapy was an independent prognostic marker for survival. A handful of retrospective studies have investigated the safety of administering targeted therapy prior to CN (10,11). Complications within 30 days were no different; however one study which included bevacizumab demonstrated increased 90-day complication rate especially wound related infections.

The authors of this study included patients with poorer performance status (ECOG >1). Previous studies in the immunotherapy era only included good performance status patients (ECOG or Karnofsky performance status ≤1% or ≥80%, respectively) including EORTC 30947 and SWOG 8949 trials. Patients with poorer performance status are unlikely to have favorable overall survival, suggesting these patients may not benefit from CN. In those retrospective studies including patients with poor performance status there is not a benefit to survival with CN.

Finally, the authors include non-clear cell type RCC. However, only 10% of the patients were non-clear cell types including papillary and chromophobe. The optimal treatment approach to patients with mRCC and non-clear cell types remains undetermined. This is in part due to many trials excluding non-clear cell patients. Additionally, papillary RCC has a distinct molecular profile distinct from cc RCC (12). In conclusion, the role and timing of CN in the era of targeted therapy remains unknown and will require further research and studies until an answer is found.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by the Editorial Board Member Dr. Xiongbing Zu (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Culp SH. Cytoreductive nephrectomy and its role in the present-day period of targeted therapy. Ther Adv Urol 2015;7:275-85.

References

1. Gershman B, Moreira DM, Boorjian SA, et al. Comprehensive Characterization of the Perioperative Morbidity of Cytoreductive Nephrectomy. Eur Urol 2016:69:84-91.
2. Tsao CK, Small AC, Moshier EL, et al. Trends in the use of cytoreductive nephrectomy in the United States. Clin Genitourin Cancer 2012;10:159-63.
3. O'Malley RL, Brewer KA, Hayn MH, et al. Impact of cytoreductive nephrectomy on eligibility for systemic treatment and effects on survival: are surgical complications or disease related factors responsible? Urology 2011;78:595-600.
4. Tomaszewski JJ, Smaldone MC, Uzzo RG, et al. Is radical nephrectomy a legitimate therapeutic option in patients with renal masses amenable to nephron-sparing surgery? BJU Int 2015;115:357-63.
5. Culp SH. Cytoreductive nephrectomy and its role in the present-day period of targeted therapy. Ther Adv Urol 2015;7:275-85.
6. Kutikov A, Uzzo RG, Caraway A, et al. Use of systemic therapy and factors affecting survival for patients

undergoing cytoreductive nephrectomy. BJU Int 2010;106:218-23.
7. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 2010;116:3378-88.
8. James AC, Lee FC, Izard JP, et al. Role of maximal endoscopic resection before cystectomy for invasive urothelial bladder cancer. Clin Genitourin Cancer 2014;12:287-91.
9. Abel EJ, Culp SH, Tannir NM, et al. Primary tumor response to targeted agents in patients with metastatic renal cell carcinoma. Eur Urol 2011;59:10-5.
10. Chapin BF, Delacroix SE Jr, Culp SH, et al. Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. Eur Urol 2011;60:964-71.
11. Wood CG, Margulis V. Neoadjuvant (presurgical) therapy for renal cell carcinoma: a new treatment paradigm for locally advanced and metastatic disease. Cancer 2009;115:2355-60.
12. Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. N Engl J Med 2016;374:135-45.

Cite this article as: Leone A, Diorio G, Zargar-Shoshtari K, Spiess PE. Comprehensive characterization of the perioperative morbidity of cytoreductive nephrectomy. Transl Androl Urol 2016;5(3):393-395. doi: 10.21037/tau.2016.03.21

