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Minerva Urology and Nephrology 2022 August;74(4):488-91
DOI: 10.23736/S2724-6051.22.05017-0

EDITORIAL COMMENT

Oncological safety of partial nephrectomy for pT3a renal cell carcinoma: reading between the lines

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on behalf of the EAU Young Academic Urologists (YAU) Renal Cancer Working Group

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In this issue of *Minerva Urology and Nephrology*, Pecoraro *et al.* sought to assess the difference in cancer-specific mortality (CSM) between partial (PN) *versus* radical (RN) nephrectomy in patients with unilateral non-metastatic pT3aN0M0 renal cell carcinoma (RCC) using data from the Surveillance, Epidemiology, and End Results (SEER) Database (2005-2016).[1] Overall, 13,177 patients were included in the analytic cohort (N.=1795 [13.6%] PN; 11382 [86.4%] RN). As expected, patients who underwent RN harbored tumors with more aggressive features (*i.e.* higher size, grade and more aggressive histology). After 1:2 propensity-score matching, 1795 patients who underwent PN were compared to 3241 patients who underwent RN. The analysis of the (measured) baseline patient- and tumor-related characteristics did not reveal statistically significant differences between the two cohorts.[1] In this cohort, cumulative incidence plots and competing-risks regression analyses revealed 5-year CSM rates of 5.0% *vs.* 10.0% (P<0.01) and 5-year other-cause mortality (OCM) rates of 5.1% *vs.* 7.5% (P<0.01) for PN and RN, respectively. At multivariable competing-risks regression analysis (after adjustment for OCM), RN independently predicted higher CSM (HR=2.10, P<0.01). The results did not change in the sub-group analysis including only patients with tumors <7 cm (N.=7187, of which 22.8% undergoing PN and 78.8% RN): also, in this subcohort, at multivariable analysis, RN independently predicted higher CSM (HR=3.1, P<0.01). The study targets an intriguing and clinically relevant research question, namely whether PN provides non-inferior onco-

logical outcomes (in terms of CSM), as compared to RN, in patients with non-metastatic (N0M0) pathological T3a RCC. Of note, answering this question might provide insights not only to refine the current decision-making schemes for nephron-sparing *vs.* radical surgery for suspected T3a RCC, but also to contextualize current guidelines recommendations on adjuvant systemic therapy for such high-risk patients.[2] Unfortunately, the interpretation of the potential benefits and harms of PN *vs.* RN for T3a RCC is challenged by the low quality of the available series.[2, 3] A recent meta-analysis of nine studies including 1278 patients treated with PN and 2,113 patients with RN for pT3a RCC showed no difference in cancer-specific survival, overall-survival and recurrence-free survival, suggesting that PN can be offered to carefully selected patients in this scenario.[3] Yet, all studies were retrospective, with a high risk of bias and confounding, critically limiting the overall quality of evidence. As such, the latest European Association of Urology (EAU) Guidelines did not provide definitive recommendations on treatment selection (*i.e.*, PN *vs.* RN) in patients with suspected pT3aN0M0 RCC.[2] The debate over the oncological non-inferiority of PN for pT3a RCC is further reinforced by the objective difficulty to preoperatively characterize renal masses suspected of locally advanced RCC in a standardized fashion.[2, 4] In fact, while routine cross-sectional imaging techniques such as contrast-enhanced computed tomography (CECT) scan or magnetic resonance imaging (MRI) can reliably diagnose gross tumor extension (or invasion) into the inferior vena cava (clinical stage cT3b-c),[5] they are less reproducible in detecting potential tumor extension into segmental branches of the renal vein, or potential tumor invasion of the pelvicalyceal system / perirenal fat / renal sinus fat (all classified as clinical stage cT3a[6]). While surgery is recommended by current guidelines for patients with locally advanced RCC,[2] such a challenging preoperative diagnosis of *cT3a*N0M0 RCC, together with the inherent heterogeneity of pT3a stage,[2, 6] may lead to a challenging interpretation of the available studies comparing the oncological outcomes of PN *vs.* RN for *pT3a*N0M0 RCC.[3] Indeed, pT3a status at histopathological analysis after PN or RN can result from two highly different preoperative clinical scenarios: either an unexpected upstage to pT3a disease from a cT1-T2 renal mass or an expected pT3a disease from a cT3a renal mass. Notably, the available (low-quality) comparative series on PN *vs.* RN for cT1 and cT2 RCC patients upstaged to pT3a RCC show contradictory results.[2] In light of the complexity of preoperative diagnosis of cT3a RCC as well as the biological heterogeneity of pT3a RCC, retrospective studies assessing the oncological outcomes of PN *vs.* RN carry a critical risk of selection bias and confounding, preventing any clinically meaningful conclusion on treatment selection in real-life clinical practice. In this regard, while Pecoraro *et al.* should be commended for their efforts to advance the field through a robust analysis of the oncological efficacy of PN for pT3a RCC, caution is needed to interpret the study results.[1] The study is limited by its retrospective design and by the well-recognized caveats of North-American population-based datasets,[7-9] including lack of granular data on patient-, tumor- and provider-related characteristics,[10] as well as on follow-up schedules and treatment patterns for local/systemic recurrence (which may significantly impact on the risk of CSM). Despite propensity-score matching, unmeasured confounders were likely the key drivers of the choice to perform PN *vs.* RN in this cohort. Among these, patient life expectancy, frailty/comorbidity status,[11] baseline renal function, as well as specific tumor features suggesting higher biological aggressiveness at preoperative imaging,[4] might have played a key role during the decision-making process. Moreover, the study results might not be entirely reproducible in different healthcare contexts and scenarios, limiting their generalizability outside the SEER reality. Lastly, the database did not allow the authors to appreciate the nuances of preoperative diagnosis of cT3a status and therefore to distinguish between the above-mentioned types of pT3a disease (*i.e.*, cT1-2 renal masses upstaged to pT3a RCC *vs.* cT3a renal masses staged pT3a after surgery). Taken together, these limitations should prompt a cautious interpretation of the oncological benefit of PN as compared to RN observed in

the study by Pecoraro *et al.*[1] Nevertheless, the study provides the opportunity to contextualize several controversial topics in the field of surgery for locally advanced RCC, and to highlight key steps that need to be taken to wind up the debate over the potential benefits and harms of PN *vs.* RN in this space. First, while waiting for liquid biomarkers and/or innovative imaging tests to refine the preoperative diagnosis and characterization of renal masses suspected of RCC,[12, 13] granular information on clinical tumor stage at CECT/MRI should be transparently reported in surgical datasets. This may allow clinicians and researchers to better depict the heterogeneity of pT3a status after surgery, aiming to assess the differential impact of tumor invasion into venous segmental branches *vs.* pelvicalyceal system *vs.* perirenal fat *vs.* renal sinus fat[6] on oncological outcomes after PN or RN. Second, considering the increasing role of adjuvant systemic immunotherapy for contemporary patients with higher-risk disease after surgery with curative intent,[2, 14] the decision to treat patients with pT3a RCC with nephron-sparing surgery rather than RN may have profound long-term implications. In fact, as the latest EAU Guidelines (weakly) recommend offering adjuvant pembrolizumab to patients with pT2G4 or pT3-T4any G or pN+any G clear-cell RCC,[2] a judicious balance between the potential increased oncological/perioperative risks of PN and its well-recognized functional benefit over RN is warranted. As such, the technical feasibility of PN (likely influenced by provider-related factors[9, 15]) should be outweighed with the risk of sub-optimal oncological outcomes, based on a comprehensive evaluation of specific tumor-related imaging characteristics suggesting adverse pathological features.[4, 12] The complexity of (suspected) locally advanced RCC, coupled with the critical impact of each step of the decision-making process on the subsequent opportunity of treatment (such as adjuvant systemic therapy) and patients' oncological outcomes and quality of life, will require implementation of dedicated workflows to offer integrated, value-based treatment strategies.[16] Centralizing treatment of locally advanced RCC at Centers of Excellence offering high-quality multidisciplinary care[17] (*i.e.*, with expert radiologists, oncologists, and surgeons) might leverage the complimentary roles of surgery and perioperative systemic therapy, hopefully improving oncologic outcomes for these patients.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Riccardo Campi, Pietro Diana and Stijn Muselaers equally contributed. All authors read and approved the final version of the manuscript.

Comment on: Pecoraro A, Amparore D, Manfredi M, Piramide F, Checcucci E, Tian Z, *et al.* Partial *vs*. radical nephrectomy in non-metastatic pT3a kidney cancer patients: a population-based study. Minerva Urol Nephrol 2022;74:445-51. DOI: 10.23736/S2724-6051.22.04680-8.

History.—Manuscript accepted: May 12, 2022. - Manuscript received: May 9, 2022.

(*Cite this article as:* Campi R, Diana P, Muselaers S, Erdem S, Marchioni M, Ingels A, *et al.*; EAU Young Academic Urologists (YAU) Renal Cancer Working Group. Oncological safety of partial nephrectomy for pT3a renal cell carcinoma: reading between the lines. Minerva Urol Nephrol 2022;74:488-91. DOI: 10.23736/S2724-6051.22.05017-0)