Editorial

Expanding thermal ablation to the 'intermediate-sized' renal mass: clinical utility in T1b tumors

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In the August 2016 issue of *European Urology*, Caputo *et al.* present the most recent series comparing outcomes of cryoablation (CA) versus partial nephrectomy (PN) for clinical T1b (cT1b) renal tumors (1). The publication retrospectively identified 31 patients at a single high-volume center who underwent percutaneous or laparoscopic CA for renal tumors >4 and ≤7 cm between 1999 and 2014. For all patients, the treating physician determined that while treatment was indicated, the risk of surgery outweighed the benefit. CA with pretreatment biopsy was performed via both laparoscopic and percutaneous approaches though the authors do not define the number of patients in each group.

Clinical, perioperative and survival outcomes were compared to 161 patients with cT1b tumors undergoing robotic-assisted PN during the same time period. Further 1:1 matching using a variation of the propensity score method was used to compare outcomes of the 31 CA patients with 31 PN patients with comparable clinical parameters, renal function and tumor complexity. Survival analysis was performed only for those diagnosed with renal cell carcinoma (RCC) on pathologic evaluation of the biopsy specimen for CA and resected tumor for PN specimens [CA: 22 pts (71%) *vs.* PN: 28 pts (90%) (P=0.085)].

There were no statistically significant differences in estimated glomerular filtration (eGFR) preservation, cancer-specific mortality and overall mortality or complication rates between the two groups. Median follow-up was longer following CA than PN (30.1 *vs.* 13 mo., P=0.008). Of patients with pathologically confirmed RCC, local cancer recurrence was significantly higher for CA compared to PN [5/22 (23%) *vs.* 0/28 (0%), P=0.019]. This has been previously observed following CA and remains the greatest concern when considering this approach (2). A critical limitation is that all tumors in the CA cohort were less than 5 cm, suggesting that findings cannot yet be extrapolated to all cT1b tumors. Other limitations include the retrospective nature, small sample size and short follow-up.

The study has several noteworthy strengths. It represents one of several recent series reporting the first outcomes of thermal ablation for tumors larger than 4 cm. The high eGFR preservation and low perioperative morbidity confirm the feasibility of ablation in increasingly larger tumors. The results are consistent with other recent series by Chang *et al.* and Thompson *et al.* who reported encouraging initial oncologic outcomes and renal preservation in cT1b tumors utilizing CA and radiofrequency ablation (RFA), respectively (3,4). An additional valuable aspect of the study was the matching to mitigate the impact of clinical profiles of patients who underwent CA. The matched groups had no statistically significant differences in age, comorbidity profile, tumor complexity or renal function allowing for a more fair comparison of clinical outcomes.

One particularly important consideration noted by the authors is that the reported results 'mainly represent outcomes for laparoscopic CA'. For the transperitoneal laparoscopic approach, Gerota's fascia is commonly incised and the retroperitoneal space is opened removing critical anatomic boundaries that limit bleeding. This concern becomes even more magnified with larger tumors as size increases the risk of bleeding after ablation (5). While the authors did not report any significant hemorrhagic complications following laparoscopic CA, these results may not be easily translatable to lower volume centers with less clinical experience. In addition, patients are subject to greater risks of anesthesia, lateral decubitus positioning and prolonged procedure times and indeed, complications are more prevalent in laparoscopic compared to percutaneous ablation (7% *vs.* 3%, P<0.5) (6).

While certain anterior and anteromedial tumors cannot routinely be safely addressed percutaneously, advances in imaging, thermal monitoring and interventional radiology expertise makes the percutaneous approach our preferred first-line method of thermal ablation for larger tumors. The authors concur with this point-of-view and note that ablative techniques are evolving and percutaneous CA is replacing laparoscopic CA as the preferred approach. Though it should be noted that a recent review of over 5,000 patients undergoing local tumor destruction between 2006 and 2010 found that 3,485 (65.9%) cases were performed laparoscopically (7).

In their final analysis, Caputo *et al.* acknowledge the higher rate of local cancer recurrence in CA for T1b tumors, and offer that this approach should remain as a second-line alternative for patients in whom treatment is indicated but are not candidates for PN. But for several reasons, the emerging literature on thermal ablation in increasingly larger renal masses should not be overlooked and there are several factors that suggest it may increase in the coming years. First, there is an increasing incidence of renal tumors and migration to lower stage disease at diagnosis creating a larger pool of patients with stage 1 renal tumors requiring management (8,9). Second, there is increased interest in active surveillance and the use of biopsy for treatment selection, particularly in the small renal mass (<4 cm) (10). This is likely to shift the focus on intervention or delayed therapy to progressively larger tumors. Third, technological advances and expertise have extended our ability to perform nephron-sparing approaches to progressively larger lesions. The integration of robotic-assisted techniques for PN and advances in imaging and ablative experience for thermal techniques continue to push the boundaries of what is technically feasible, increasing the role of nephron-sparing interventions for patients who were historically only candidates for nephrectomy (11,12).

While the potential for ablative techniques for cT1b lesions is evident, there are significant limitations that must be considered. The efficacy of thermal ablation was established in renal masses ≤3 cm and complications have been shown to increase with increasing tumor size and increasing number of probes used (5,13). Several studies have highlighted the diminishing efficacy of ablation with increasing tumor size. Best *et al.* reviewed long-term outcomes of primary radio frequency ablation in 159 patients with tumors ranging from 0.9 to 5.4 cm and noted that disease-free survival was dependent on size (14). The three year disease-free survival rate was 96% for tumors less than 3 cm compared to 79% for those greater than 3 cm (P=0.001). Similarly, Psutka *et al.* reviewed long-term outcomes of RFA in 185 patients and noted that tumor stage was the only predictor of disease free survival with local recurrence of 4.2% for cT1a tumors compared to 14.3% for cT1b lesions (P=0.0196) (15). While Thompson *et al.* recently reported 3-year disease free survival of 97% after CA for cT1b lesions, the 5-year DFS of 81% reported by Chang *et al.* and local recurrence-free survival of 77% reported by Caputo *et al.* are more consistent with the previous ablation literature. Local recurrence after PN for T1b lesions has been reported from 1–9% (16).

It is also important to note that renal tumors should not be evaluated by size alone. Anatomic complexity affects the biologic behavior, surgical approach, therapeutic efficacy and risk of complications associated with thermal ablation and has an 'invisible' influence on case selection that may not be evident in retrospective studies. Anatomic complexity correlates with behavior with more complex lesions exhibiting more aggressive growth patterns, independent of size (17). Centrally located tumors near the hilum are also subject to a 'heat-sink effect' with diminished energy delivery to target tissue diminishing ablation (18). Further, closer proximity to the renal sinus, larger vessels, collecting system and proximal ureter increases the risk of complications such as hemorrhage, urine leak or ureteral injury that limits the number of probes and placement choices to achieve complete ablation. Indeed objective complexity scoring system have proved to be superior to size alone in predicting operative times, estimated blood loss and perioperative complications for ablation (19). As in many ablative series, the CA patients in the overall Caputo *et al.* cohort were less anatomically complex as rated by Nephrometry score compared to those that had PN {CA: 8 [6–9] *vs.* PN: 9 [8–10] P=0.007} likely reflecting the preference for ablation in more peripheral, exophytic lesions.

One final point worth considering in ablation of larger tumors is the integration of a more structured approach to pre-treatment risk stratification. Patients undergoing percutaneous biopsy in the CA arm by Caputo underwent fine needle aspiration rather than core biopsy and 8 patients (25.5%) who underwent ablation had benign or oncocytic pathology. Interestingly, a survey of urologists performing ablations noted that while peri-procedural biopsy was 89%, pathology results were only available in advance to guide decision making in 19% of cases (20). Thus it appears that the current practice is to proceed with 'intent-to-treat' for renal tumors, without integrating results of the biopsy into management. Contemporary guidelines support the use of percutaneous biopsy in a systematic fashion to define pathology prior to ablation, with the results used to guide clinical decision-making (21,22).

The addition of the recent series on ablation for cT1b tumors is encouraging but we must proceed with caution to determine those patients most likely to derive benefit while mitigating the risks of intervention. In appropriate situations, observation or expectant management is a reasonable approach for patients with significant co-morbidities, particularly as the risk of intervention increases with the size of the tumor. Recent nomograms are emerging to better objectively define those most likely to benefit from ablative techniques based on predicted surgical risks (23). Percutaneous biopsy should also be used systematically, with results available before proceeding to ablation, to consider monitoring of patients with non-malignant pathology. We must consider more than size alone in planning treatment as complexity affects both efficacy and complication risk. Thus current staging based on size alone may not be optimal for selecting patients for various treatments. And we should strive to collaborate with colleagues in interventional radiology to harness the potential of more precise imaging modalities, thermal monitoring and increasing operator experience to expand the pool of candidates eligible for ablation (12).

We believe that in the coming years we will continue to optimize risk stratification and patient selection, further standardize the ablative approach and see increasing benefits from advancements in ablative technologies and expertise. Thus as we consider expanding the role of ablation, we must proceed cautiously to maximize the therapeutic benefits, while minimizing risks to our patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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