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Perioperative, oncological and functional outcomes after robotic partial nephrectomy vs. cryoablation in the elderly: A propensity score matched analysis

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Abstract

Objective: To compare perioperative, oncological and functional outcomes of robotic partial nephrectomy (RPN) versus cryoablation in elderly patients (>75 years old), accounting for patient's and tumor's related factors.

Methods: Retrospective institutional review of 312 consecutive elderly patients (> 75 years old) who underwent RPN or cryoablation for renal mass (June 2006−December 2016).

Demographic, perioperative, functional, and oncological data were evaluated. Sixty-five patients who underwent RPN were propensity-score matched 1:1 to 65 who underwent cryoablation (matching was based on demographics, renal function, comorbidities and tumor characteristics). Perioperative outcomes were compared. Survival analysis was performed to estimate overall (OS), recurrence-free (RFS) and cancer-specific survival (CSS) by Kaplan-Meier method. A linear mixed effect model (LME) estimated the effect of follow-up on estimated glomerular filtration rate (eGFR).

Results: After matching, the variables were well balanced with no differences at baseline between groups. Shorter operative time and lower blood losses favored cryoablation (140 vs. 200 min, $P < 0.0001$ and 100 vs. 195 ml, $P = 0.0002$, respectively). Overall complications rate was higher for RPN (31% vs. 9%; $P = 0.007$), but no difference was found in major (Clavien III-IV) complications (6% vs. 1.5%, $P = 0.2$).

At a median follow-up of 37 (29−44) and 46 (38−53) months for RPN and cryoablation, no significant differences were found in CSS (100% vs. 95%, $P = 0.3$) and OS (80% vs. 75%, $P = 0.2$) but RFS was higher for RPN (100% vs. 83%, RPN vs. cryoablation, respectively, $P = 0.02$). eGFR was comparable between the groups at every time point analyzed.

Conclusions: Although with a higher rate of recurrences, our data confirm cryoablation as a lower morbidity profile treatment option for small renal masses in the elderly population, with cancer-specific survival comparable to surgery. © 2018 Elsevier Inc. All rights reserved.

Keywords: Robot; Partial nephrectomy; Cryoablation; Renal neoplasm; Elderly; Nephron-sparing

1. Introduction

Robotics has now matured into an excellent approach for performing partial nephrectomy (PN) for renal masses [1], but the management of localized renal masses still remains a controversial topic. Nephron sparing surgery is recommended whenever possible by the current guidelines. Nevertheless, several factors should be considered during patient's counseling, including comorbidities, oncologic potential of the mass, functional issues and potential treatment-related morbidity [2].

The debate is particularly heated in the subgroup of the elderly patients (>75 years old), given the higher surgical risk of undergoing PN in these particularly frail surgical candidates [3].

A SEER data analysis comparing surgical vs. nonsurgical approaches to renal masses failed to demonstrate a benefit from surgical treatment in cancer specific survival for patients over 75 years old [4]. By contrast, a similar analysis on cT1a only patients older than 75 demonstrated an increased cancer specific mortality for nonsurgical approaches [5].

A recent single-institutional analysis of patients with cT1a renal masses including 1,057 patients who underwent PN, 180 who underwent radiofrequency ablation, and 187 who underwent cryoablation, showed similar local recurrence-free survival among the three treatment modalities, whereas metastases-free survival was significantly better after PN and cryoablation. In both the cT1a and cT1b groups, PN patients were significantly younger, with lower Charlson's scores and had superior overall survival. Moreover, the study was flawed by not matching for tumor complexity and significantly more malignant histology in the PN cohort [6].

In this setting and particularly in the elderly patients unfit for surgery, the recently published American Urological Association's guidelines about localized renal cancer have underlined how active surveillance ideally preceded by renal biopsy should be considered as initial treatment option for small renal masses suspicious for cancer [2].

Trying to contribute to this controversial topic, we designed the present study.

Robotic PN versus cryoablation for renal mass in elderly patients were compared focusing on perioperative, oncological, and functional outcomes. To increase the value of the present report, a propensity-score matching was included accounting for patient's and tumor's related factors.

2. Materials and methods

A retrospective review of 312 consecutive elderly patients (>75 years old) who underwent robotic PN or cryoablation (either laparoscopic or CT-scan guided percutaneous) for renal tumor at our institutions was performed (June 2006−December 2016). Additional data of interest pertaining to long-term outcomes were eventually obtained via direct mailing with patients and their local clinics after appropriate IRB approval.

2.1. Outcome measurements and statistical analysis

2.1.1. Propensity score matching

General characteristics of the treatment groups at baseline were summarized with means and standard deviation for continuous variables including age, body mass index (BMI), ASA score, Charlson's Comorbidity Index, clinical tumor size, R.E.N.A.L. score and preoperative serum creatinine and frequency counts and percentages for the categorical variables including sex, race, clinical T stage, diabetes, hypertension and pre-existing chronic kidney disease (CKD, defined as preoperative estimated glomerular filtration rate [eGFR] <60 ml/min).

Student's t test was used to compare means of continuous variables by treatment groups. Chi-square test was used to compare the frequency of categorical variables by treatment groups.

Of 312, 16 (5.1%) patients were excluded because of missing in those covariates, leaving 296 patients (94.9%). Using a logistic regression model, propensity score for robotic PN was calculated using the covariates among 296 patients. Of the 296 patients, 45 patients were excluded because their PS did not fall in the common region of the 2 treatment groups, remaining 251 patients.

The propensity scores of the 2 treatment groups were then matched from nearest neighbor (greedy matching algorithm) in a ratio of 1:1 with no replacement. Sixty-five patients who underwent robotic PN were matched to 65 patients who underwent cryoablation (33 + 32 performed via a laparoscopic and a percutaneous approach, respectively) according to age, sex, race, BMI, ASA score, diabetes, hypertension, pre-existing CKD, Charlson's Comorbidity Index, clinical tumor size, R.E.N.A.L. score and preoperative serum creatinine.

2.1.2. Outcomes

2.1.2.1. Perioperative. Perioperative outcomes, including procedure time, blood loss, length of stay, and complications (either intraoperative or postoperative) were compared between the groups. Postoperative complications were classified using the Clavien system and grouped into low-grade (grades 1−2) and high-grade (≥ 3) complications [7].

2.1.2.2. Oncological. Pretreatment biopsy was performed in all patients who underwent cryoablation. Percentage of malignancies was calculated, and Fuhrman grading reported in case of confirmed malignancy. Tumor recurrence in the cryoablation group was defined as an area of new contrast enhancement within a previous completely treated ablation site appearing >3 months after treatment. The RPN group underwent renal cross-sectional contrast-enhanced imaging within 3−12 months after surgery, and annually thereafter. Tumor recurrence in the RPN group was defined as a new contrast-enhancing lesion found within or abutting the surgical resection bed for the ipsilateral kidney.

Survival analysis was performed in patients who were diagnosed with renal cell carcinoma in resected tumor (at PN) or after tumor biopsy (in cryoablation group) at final pathology. Overall (OS), recurrence-free (RFS), and cancer-specific survival (CSS) were analyzed using the Kaplan-Meier method. Comparisons by treatment groups were performed by log-rank test.

2.1.2.3. Functional. Serum creatinine and eGFR data were collected at baseline and at multiple time points postoperatively. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate GFR [8].

A linear mixed effects (LME) model was used to assess eGFR at each follow-up for matched patients. Follow-up was

treated as a factor variable to account for nonlinear time trends. After modeling, contrast analysis was used to compare robotic PN vs. cryoablation patients at each follow up point (at 1 day, 3 days, 1 month, 3 months, 6 months, and 12 months postoperatively) using Sidak-Holms P value adjustments for multiple comparisons. Statistical analyses were performed in R (version 3.4.4., R Project for Statistical Computing, Vienna, Austria) reporting and interpretation of the results was conducted according to established guidelines [9].

3. Results

At prematching comparison, a significant difference between robotic PN and cryoablation patients was found in age, BMI, ASA score, percentage of patients with diabetes, clinical tumor size and T stage, R.E.N.A.L. score and preoperative creatinine ($P \leq 0.03$) (Supplementary Table 1).

After matching, the variables were well balanced with no differences at between the groups in age (79.3 vs. 79.3 years, $P = 1$), BMI (27.4 vs. 27.9 kg/m^2, $P = 0.6$), ASA score (3 vs. 2.9, $P = 0.5$), patients with diabetes (38% vs. 41%, $P = 0.7$), tumor size (2.9 vs. 3.0 cm, $P = 0.9$), T stage distribution ($P = 0.8$), R.E.N.A.L. score (6.9 vs. 6.4, $P = 0.1$) and serum creatinine (1.2 vs. 1.3 mg/dl, p = 0.7), robotic PN vs. cryoablation, respectively (Table 1).

Regarding the perioperative outcomes, shorter operative time and lower blood losses favored laparoscopic cryoablation (140 vs. 200 min, $P < 0.0001$ and 100 vs. 195 ml, $P = 0.0002$, respectively).

No differences were found in intraoperative complications. Overall complications rate was significantly higher for PN (31% vs. 9%; $P = 0.007$). After stratification, Clavien I-II complications rate remained significantly higher for PN (25% vs. 8%, $P = 0.009$) but groups were comparable in major (Clavien III-IV) complications (6% vs. 1.5%, $P = 0.2$) (Table 2).

As concerning the oncological data, 54 (83%) vs. 48 (74%) lesions were malignant at final pathology ($P = 0.02$). No differences were found in the distribution of Fuhrman grading between the groups (Fuhrman grades 1−2: 44% vs. 42%, $P = 0.3$). At a median follow-up of 37 (29−44) and 46 (38−53) months for PN and cryoablation, respectively, no significant differences were found in CSS (100% vs. 95%, robotic PN vs. cryoablation, respectively, $P = 0.3$) and OS (80% vs. 75%, robotic PN vs. cryoablation, respectively, $P = 0.2$) between the groups even though recurrence free survival was significantly higher for PN (100% vs. 83%, robotic PN vs. cryoablation, respectively, $P = 0.02$) (Fig. 1 and Supplementary Fig. 1). Among the patients who were diagnosed with recurrence after cryoablation, 6 underwent repeat ablation whilst 2 remained under active surveillance.

Analyzing the functional outcomes, eGFR was comparable between the groups at every time point analyzed (Fig. 2). Based on contrast analysis (Table 3), there were no significant differences in eGFR between the two treatment groups at any of the measured time points. eGFR was comparable for both groups before operation and remained comparable across the postoperative course.

4. Discussion

Based on our findings, both robotic PN and cryoablation can be considered as treatment options for solitary, localized, small renal mass in the elderly population. Overall, robotic PN had higher rate of perioperative morbidity likely due to the frailty of this population, but it was comparable to cryoablation regarding the major complications.

On the other side, a higher probability of local cancer recurrences was found after cryoablation. The two approaches were comparable in the functional outcomes along the 12 months follow-up considered.

Thermal ablation procedures including cryoablation and radio-frequency ablation have been developed aimed to improve the morbidity profile of nephron-sparing approaches. Namely, they allow for reducing the risk of complications and avoiding renal ischemia [10].

Among ablative procedures, cryoablation has showed several potential benefits compared to PN, with a low morbidity profile and an excellent oncological control [11−13].

Unfortunately, the available evidences are mainly based on single-institutional studies with many limitations including retrospective design, small sample size, lacking patient's information and short follow-up [13].

A special reference needs to be made to the role of ablative procedures in the elderly.

According to current guidelines, ablation is a treatment option for cT1 tumors and can be offered to the elderly and/ or comorbid patients, with limited life expectancy [2,14].

Indeed, a retrospective population-based analysis of 42,000 patients in the United States who were treated with (PN) or radical nephrectomy for renal cell carcinoma, Bianchi et al. found other-cause mortality rates nonnegligible in elderly patients (≥70 years), even at low-grade, low stage disease [15].

In the present study, we aimed to perform a dedicated comparative analysis of cryoablation vs. robotic PN in this specific subgroup of patients. Notably, we assessed together the complications, the oncological and the functional outcomes.

Our data confirmed available literature underlining the lower morbidity profile favoring cryoablation [10,16]. In the most recently published quantitative synthesis on more than 700 patients, when compared with minimally-invasive PN, laparoscopic cryoablation was associated with significantly lower risk of total (Relative Risk = 1.82), urological (RR 1.99) and nonurological complications (RR 2.33). In this analysis limited to >75 years old patients we found no significant difference in major postoperative complications.

Such data were confirmed at our pre-matching analysis performed on 120 vs. 192 patients (cryoablation vs. PN patients, respectively), but interestingly 13 out of 120 cryoablation patients had complications (11%) vs. 40 out of 192 robotic PN patients (21%). The difference was still statistically significant but less marked ($P = 0.04$).

Table 1
Characteristics of the treatment groups after propensity score matching

Characteristic	Robotic partial ($n = 65$)	Cryoablation ($n = 65$)	P value*
No. (%)			
Sex			
Female	22 (34)	27 (40)	
Male	43 (66)	38 (60)	0.4
Race			
African−American	7 (11)	5 (8)	
Caucasian	58 (89)	59 (91)	0.8
Hispanic/Latino	0 (0)	1 (1)	
Other	0 (0)	0 (0)	
Clinical T			
T1a	55 (85)	54 (83)	0.8
T1b	10 (15)	11 (17)	
T2a	0 (0)	0 (0)	
T2b	0 (0)	0 (0)	
T3a	0 (0)	0 (0)	
Diabetes	25 (38)	27 (41)	0.7
Hypertension	50 (77)	46 (71)	0.4
Pre-existing CKD	31 (48)	33 (51)	0.7
Mean (SD)			
Age, years	79.3 (3.3)	79.3 (4.1)	1
BMI	27.4 (4.9)	27.9 (5.9)	0.6
ASA score	3.0 (0.5)	2.9 (0.6)	0.5
Charlson's Comorbidity Index	2.0 (1.5)	2.3 (1.6)	0.3
Clinical tumor size, cm	2.9 (1.0)	3.0 (1.0)	0.9
R.E.N.A.L. score	6.9 (1.9)	6.4 (2.0)	0.1
Preoperative creatinine, mg/dl	1.2 (0.4)	1.3 (0.5)	0.7

  * P value for difference in means by treatments was calculated using two-sides t-test and the difference in frequency were calculated using chi-squared test;
     P value for race was calculated by comparing Caucasian with others and for clinical T was calculated by comparing clinical group T1a with others.

Table 2
Perioperative outcomes

Characteristic	Robotic partial ($n = 65$)	Cryoablation ($n = 65$)	P value
No. (%)			
Intraoperative complications	2* (3)	1** (1.5)	0.5
Postoperative complications	20 (31)	6 (9)	0.007
Clavien I-II			
	3 Fluid overload	1 Urine leak	0.009
	3 Atrial fibrillation	3 Hematoma	
	3 Acute renal failure	1 Pneumothorax	
	1 Desaturation		
	2 Acute urinary retention		
	1 Hyperkalemia		
	2 Bleeding		
	1 Pneumonia		
	Tot. 16 (25)	Tot. 5 (8)	
Clavien III-IV			
	2 Respiratory insufficiency	1 Bleeding + acute renal failure	0.2
	1 Cardiorespiratory arrest		
	1 Urosepsis		
	Tot. 4 (6)	Tot. 1 (1.5)	
Mean (SD)			
Operative time, min***	200 (50)	140 (60)	<0.0001
Blood loss, ml***	195 (139)	100 (140)	0.0002
Length of stay, days	4 (2)	1 (1)	<0.0001

  * 1 Mesentery injury at Veress needle insertion, 1 liver laceration − both treated conservatively.
  ** 1 spleen laceration - treated conservatively.
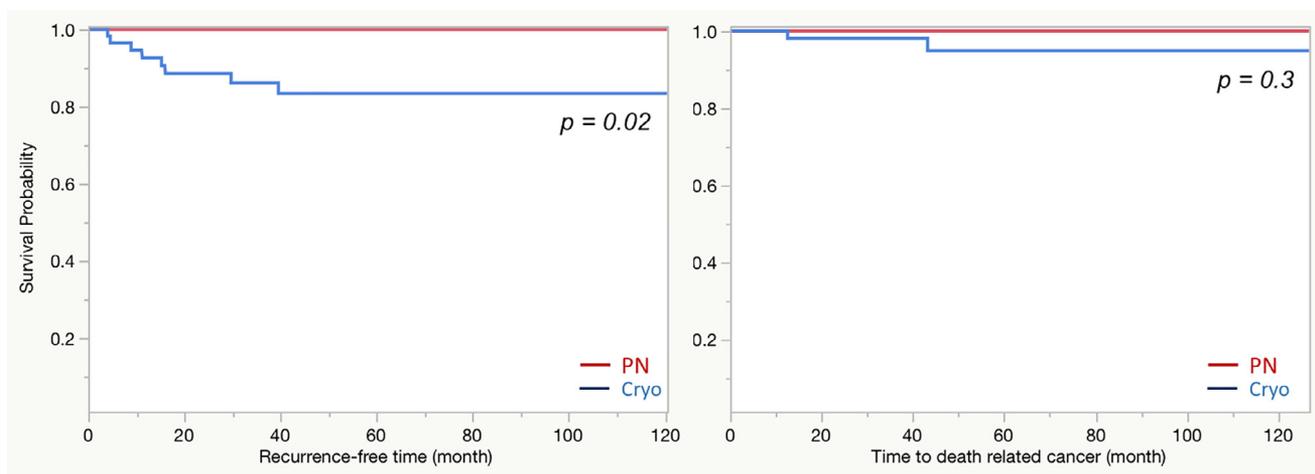 *** Data from 33 laparoscopic cryoablations in the cryoablation treatment group.

Fig. 1. Cumulative incidence curves (Kaplan-Meier method) showing recurrence-free survival (RFS) and cancer-specific survival (CSS). Five years RFS estimate is 83% and 100%, robotic PN vs. cryoablation, respectively. Five years CSS is 100% vs. 95%, robotic PN vs. cryoablation, respectively (reported P values from Log-rank test).
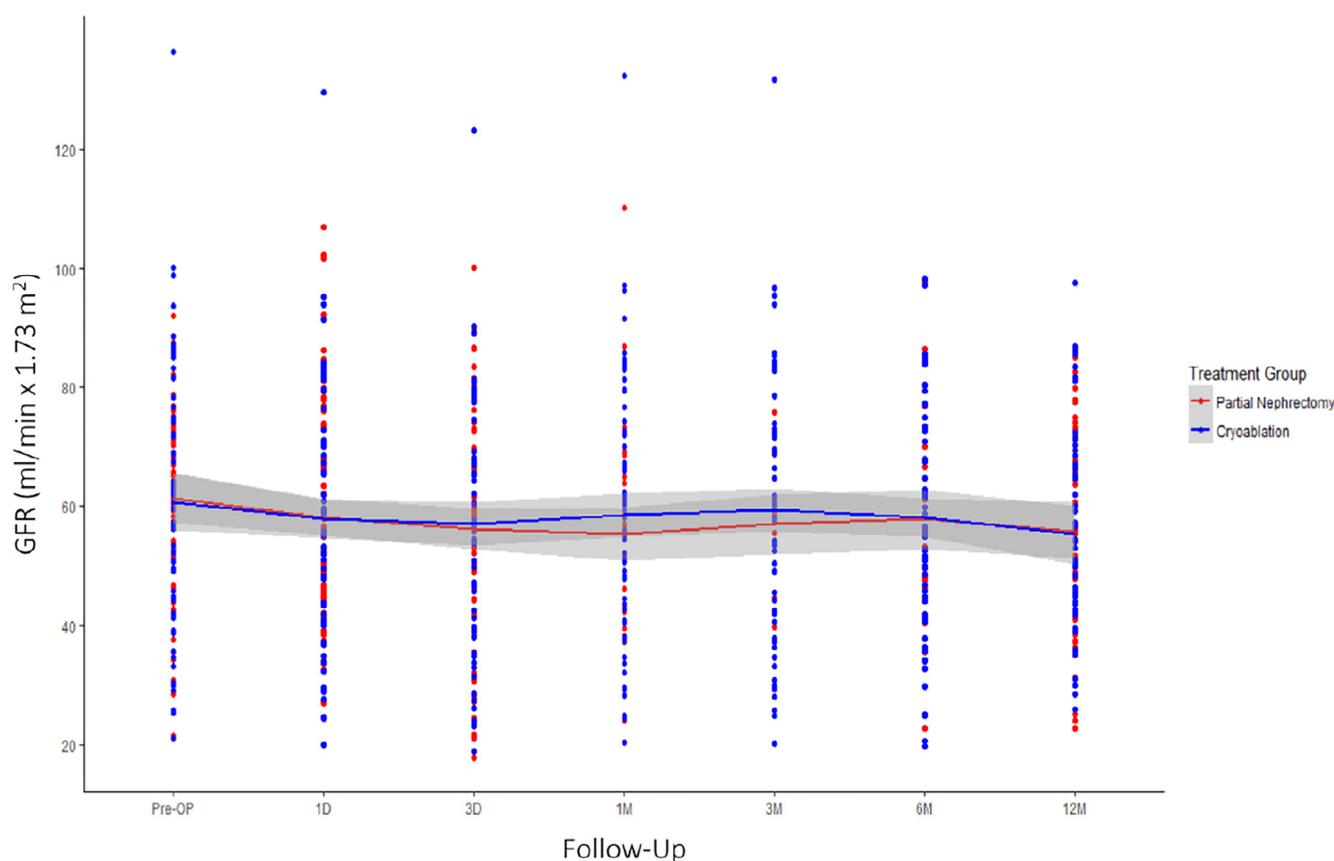

Fig. 2. Estimated glomerular filtration rate (eGFR) for matched patients receiving either robotic partial nephrectomy or cryoablation. Patient's eGFR is plotted for each measured follow-up point (preoperative, 1 day, 3 days, 1 month, 3 months, 6 months, and 12 months). Lines represent the LOESS smoothed time trend for each treatment type with gray bands representing the confidence interval for the fitted trend line.

Regarding the oncological outcomes, we found no significant differences between the treatment groups in terms of CSS ($P = 0.27$) and OS ($P = 0.25$). A higher rate of local recurrences was found for cryoablation ($P = 0.02$). We acknowledge a significantly longer median follow-up for cryoablation (46, IQR 38−53 vs. 37, IQR 29−44 months,

cryoablation vs. PN, respectively, $P < 0.001$). On the other side, the more recent institutional analysis on a cohort of patients with a minimum 5-year follow-up after robotic PN confirmed low recurrence rates after robotic PN, with 3.6% and 4% 5- and 7-year cumulative incidences of local recurrence, respectively [17].

Table 3
Estimated glomerular filtration rate (eGFR) differences between cryoablation and robotic partial nephrectomy (PN) in matched treatments groups

Comparison time point	Estimated eGFR difference (Cryoablation vs. PN)	95% CI	Adjusted P value
Preoperative	−0.4	−9; 8.2	1
1 day	−1.3	−10; 7.5	1
3 days	0.8	−7.5; 9	1
1 month	2.8	−6; 11.5	1
3 months	2.5	−7.8; 12.7	1
6 months	1.9	−7; 10.8	1
12 months	1.2	−6.5; 8.9	1

eGFR was measured preoperatively and at 6 follow-up points postoperatively. Contrast analysis was used to generate estimated differences between treatment groups of matched individuals at each given time point. Estimates are given with the corresponding lower and upper confidence limits of the 95% adjusted confidence interval (CI). P values were adjusted using the Sidak−Holms method and were presented in the final column.

Literature has evolved in the considerations on the oncological effectiveness of cryoablation.

In 2014 Klatte et al. reported fair evidence that oncological outcomes are substantially worse for cryoablation than for minimally-invasive PN [16], with a higher risk of local recurrence after cryoablation (RR 5.24, 95% confidence interval [CI] 2.67−10.28). Similarly, a meta-analysis by Kunkle et al. identified a higher risk of local recurrence for cryoablation (RR 7.45, 95% CI 2.24−6.92) [18]. Of note, none of the analyses by Klatte et al. and Kunkle et al. did account for patients' clinical T stages.

Conversely, a single-institutional analysis by Thompson showed similar local recurrence-free survival between PN and cryoablation, but the study was flawed by no matching for tumor complexity and significantly more malignant histology in the PN cohort [6]. In line with Thompson's findings, in the updated quantitative synthesis of oncological outcomes after PN vs. cryoablation, D'Andrea, Shariat, and Klatte reported excellent long-term oncological outcomes for cryoablation of renal tumors, similar to those of PN, in properly selected patients. Their data confirmed our personal experience in the overall population [19].

Regarding renal functional outcomes, our results confirm in the elderly population that both cryoablation and robotic PN have a minor impact on renal function [20]. In the most recently published matched analysis, Bhindi et al. performed a comparison between patients undergoing PN vs. cryoablation for tumor in solitary kidney. After accounting for potential confounders, the authors found no significant differences in eGFR drop from baseline to discharge (11% vs. 16%, $P = 0.2$) and from baseline to the third postoperative month (12% vs. 9%, $P = 0.3$, cryoablation vs. PN) [21].

We underline that in the present analysis the mean tumor size of treated lesions was 3 cm, at the edge of the comfort zone for cryoablation. We previously demonstrated that patients treated with cryoablation for larger tumors had a significantly higher rate of local cancer recurrence [22].

We acknowledge the limitations of the study. First, it was a retrospective study, with inherent bias. Although we accounted for key patient's and tumor's variables by the matching process, it is possible that selection bias or confounders inherent to retrospective analysis exist for which we were unable to control. On the other hand, we underline the very selected population the study was focused on.

Second, we did not discriminate between percutaneous and laparoscopic-assisted approach for cryoablation. It is reported that laparoscopic ablation has higher rate of complications when compared with percutaneous approach. In a recent meta-analysis, Pessoa et al. reported 3.1% vs. 7.4% rates of complications in the percutaneous vs. laparoscopic group, respectively [23].

Finally, 20% to 25% of patients received treatment for benign masses. Unfortunately, the propensity-score matching was based on preoperative tumor's characteristics and did not prevent from the finding of a higher proportion of patients found with malignant lesions at final pathology after partial nephrectomy.

This could represent a bias and/or reflect the nonsystematic indication to biopsy in patients who underwent ablative treatment.

Lastly, we underline that caution is required before drawing conclusions based on populations with small sample sizes combined with the low number of events for cancer recurrence.

Notwithstanding the limitations, the results obtained from the present analysis are in line with the most recent American Urological Association's guidelines recommendations [2]. We consider cryoablation a reliable alternative for the management of cT1a renal masses <3 cm in size. The percutaneous approach should be preferred as the real challenger for RPN, due to the much lower morbidity profile. Renal tumor biopsy should be performed prior to cryoablation. Clearly, the patient counseling for cryoablation should include information regarding the increased likelihood of tumor recurrence after primary treatment, which may be addressed with repeat treatments if needed. There are several patient-related and tumor-related factors arguing for surgery [2,24]. Among patient's factors, a long life expectancy, low comorbidities and perioperative risk, a good renal functional reserve and lastly patient's choice represent key criteria. Tumor size >3 cm, tumor growth >5 mm per year, high complexity and infiltrative pattern at pretreatment imaging and unfavorable pathology findings in patients who undergo renal biopsy represent paramount tumor factors.

An appropriate patient selection and counseling for alternatives to treatment (i.e. biopsy and surveillance), particularly in the elderly patients in which the competing risk of noncancer related death is higher, is mandatory.

5. Conclusions

Our data confirm the role of cryoablation as a treatment option for solitary, localized, small renal masses in the elderly population. In our institutional analysis, after controlling for

potential confounders, such an approach had significantly lower morbidity profile and similar renal functional outcomes compared to robotic partial nephrectomy. Notwithstanding the lower rate of malignancies, a higher likelihood of recurrence was found after cryoablation, but cancer-specific survival was comparable to that of the surgical treatment.

Conflict of interest

Jihad H. Kaouk certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. Employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patent filed, received or pending) are the following: Endocare, Inc, Intuitive

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2018.12.016.

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