Oncological outcomes of active surveillance and percutaneous cryoablation of small renal masses are similar at intermediate term follow-up

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ABSTRACT

BACKGROUND: Active surveillance (AS) and minimally invasive ablative therapies such as percutaneous cryoablation (PCA) are emerging as alternative treatment modalities in the management of small renal masses (SRMs).
METHODS: Fifty-nine patients underwent PCA since 2011 and 75 underwent AS since 2010 at two different institutions. Only patients with follow-up ≥6 months were included. All patients were followed with a standardized protocol. Treatment failure was defined by dimensional progression for AS and renal recurrence for PCA, in addition to stage and/or metastatic progression for both groups.
RESULTS: Treatment failure was observed in 14 cases (18.7%) during AS (mainly due to dimensional progression) and 12 patients (16%) underwent delayed intervention with a mean follow-up of 36.83 months. Seven patients (11.9%) in the PCA group experienced treatment failure with a mean follow-up of 33.39 months and three of them underwent re-ablation successfully. Cancer-specific-survival at 2 and 5 years was 100% and 95,8% in AS-group *vs*. 98.2% and 98.2% in PCA-group (P=0.831). One patient in both groups died from metastatic disease. Overall-survival at 2 and 5 years was 91.7% and 82.4% in the AS group *vs*. 96.5% and 96.5% in the PCA group (P=0.113). Failure-free survival at 2 and 5 years was 90.9% and 70.1% in the AS group *vs*. 93.1% and 70.9% in the PCA group (P=0.645).
CONCLUSIONS: AS and PCA provide similar survival outcomes and are safe and valid treatment options for elderly and comorbid patients with SRMs.

KEY WORDS: Watchful waiting; Cryosurgery; Kidney neoplasms; Renal cell carcinoma.

Although partial nephrectomy (PN) is the gold standard treatment for organ confined renal masses, active surveillance (AS) and minimally invasive ablative therapies such as cryoablation and radiofrequency ablation are emerging as alternative treatment modalities aiming to reduce morbidity and minimize the risk of renal function impairment.[1-4]

Active surveillance is defined as the initial monitoring of a small renal mass (SRM) by as-

sessment of tumor growth at serial abdominal imaging, with delayed intervention reserved to masses showing clinical progression during follow-up.[5] Active surveillance can be offered to patients unfit for or refusing surgery and to elderly and/or comorbid patients at increased risk of competing-cause mortality.[1, 6, 7] In the largest AS cohorts the growth of SRMs is slow in most cases and progression to metastatic disease is rare (1-2%).[8-10]

Cryoablation and radiofrequency ablation are the most common ablative techniques for the treatment of renal tumors.[1] Cryoablation can be performed using either a percutaneous or a laparoscopic approach.[11] The former has been described to have a lower major complication rate, while the latter allows less incomplete tumor ablations and potentially a better cancer-specific survival rate.[11]

Local failure of AS and percutaneous cryoablation (PCA) are defined by dimensional progression and renal recurrence, respectively.[8, 12] In these cases interventional and often invasive procedures are needed to obtain local control and potentially improve survival.

Currently, there are no studies that directly compared the oncological outcomes of active surveillance and cryoablation in the treatment of small renal masses (SRMs). This information is important for clinical decision making in this setting. The current study aims to compare treatment failure and survival outcomes in two cohorts of patients with SRMs managed with AS and PCA at two academic institutions.

Materials and methods

Patient population

Overall, 134 patients with a single cT1a renal tumor from two large academic Italian centers were included in the study. Only patients currently enrolled in ongoing prospective protocols with a minimum follow-up of 6 months were included. Seventy-five patients (AS group) were consecutively enrolled in a structured and standardized AS protocol at the Department of Urology, Maggiore della Carità Hospital in Novara since 2010, while 59 patients (PCA Group) were consecutively treated with percutaneous cryoablation at the University Hospital of Trieste since 2011.

Interventions

Active surveillance

Patients enrolled in the AS protocol were followed with a standardized follow-up schedule including serial abdominal imaging every 6 months in the first three years and annually thereafter. Contrast-enhanced triphasic CT scan or MRI were preferred, but abdominal ultrasound (US) was accepted in cases with good ultrasound visibility and dimensional stability of the renal mass over time. Chest imaging was performed at all follow-up visits in order to identify lung metastases. A chest CT was always obtained when an abdominal CT was performed, while a chest x-ray was performed in the other cases.

Percutaneous renal tumor biopsy (RTB) was discussed with all patients after clinical diagnosis but performed in selected cases. It was not recommended for renal masses <15 mm or with unfavourable tumor location for the lower probability to obtain a diagnostic result and/or the higher risk of complications, for patients with severe comorbidities contraindicating a potential delayed intervention or for those taking antiaggregant or anticoagulant drugs in order to avoid the risk of bleeding.

A good compliance to the follow-up protocol was ensured through a careful screening of patients attending the follow-up appointments at a dedicated AS clinic. All data were prospectively collected in a dedicated database. Patients with progression and/or willing to quit AS were counselled to undergo delayed intervention with minimally invasive ablative therapy or surgery.

Cryoablation

Cryoablation was performed in all cases by a single dedicated interventional radiologist with experience in percutaneous ablative procedures. A percutaneous approach under CT guidance using the Visual-ICE System (Galil Medical) was adopted. In order to construct a three-dimensional therapeutic isotherm that covers the target lesion, 2 to 4 sealed argon 17-G cryoprobes were

used. Post-procedural helical CT scan images were acquired to confirm the ablation zone and to exclude immediate complications such as bleeding or urine leak. Percutaneous RTB was always discussed and frequently performed prior to ablation.

The follow-up protocol was standardized and based on the recommendations of the American College of Radiology.[12] Follow-up imaging with a dedicated renal mass protocol with contrast-enhanced CT or MRI was used. An early scanning within 1 month of PCA was performed in all patients in order to rule out inadequate treatments. Follow-up imaging was performed at 3, 6, and 12 months during the first year, every 6 months up to three years and annually thereafter. Chest imaging with chest CT or X-ray was performed at all follow-up visits in order to identify lung metastases. In the event of local recurrence patients underwent either repeat PCA or surgery.

Definition of treatment failure

Failure of AS was defined as dimensional progression (tumor volume doubling time <12 months and/or tumor maximum diameter >4 cm at imaging) or clinical progression (increase in TNM stage, development of distant metastasis, new onset of symptoms clearly related to renal tumor). Failure of PCA was defined as local recurrence (onset of contrast enhancement in the ablation field and/or enlargement of the ablated tumor at ≥3 months after a successful ablation) or clinical progression as defined above.[8, 12]

Study endpoints

The primary endpoint of the study was cancer specific survival (CSS). Secondary endpoints were overall survival (OS) and treatment failure-free survival (FFS) defined as the time from the diagnosis of the renal mass to the date of the imaging showing treatment failure. In the PCA group complications were also assessed and classified according to the Clavien-Dindo classification.

Statistical analysis

Statistical analysis was performed using SPSS v. 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean and standard deviation while categorical variables were reported as frequencies and proportions. The Chi-square test and *t*-test were used to compare categorical and continuous variables respectively ($P<0.05$). Survival analysis was performed using the Kaplan-Meier method.

Results

Overall, 134 patients were included in the study. Seventy-five patients were managed with AS and 59 with PCA. The demographic and clinical characteristics of patients and SRMs in the two cohorts are displayed in Table I. There were more patients with a Charlson Comorbidity Index (CCI) of 0 in the PCA group (35.6 *vs.* 20%, P=0.043). Tumor size was not significantly different in the two groups (19.52 in the AS group *vs*. 22.20 in the PCA group, P=0.071). Ten tumors (13.3%) were cystic in the AS group, while all tumors were solid in the PCA group (P=0.004). Percutaneous renal biopsy was performed in a significantly higher proportion of patients in the PCA group compared to the AS group (91.5% *vs.* 25.3%, P<0.001). Biopsy proven histology was equally distributed between groups, with 76.9% and 81.6% of the tumors being RCCs in the AS and PCA group, respectively (P=0.715). Mean follow-up was similar (36.83 months in the AS group *vs.* 33.39 months in the PCA group, P=0.353).

Patterns of treatment failure and delayed intervention are reported in Table II and Figure 1. In the AS group, treatment failure occurred in 14 patients (18.7%). Failure was represented by dimensional progression in the majority of cases (85.7%). Clinical symptoms (gross hematuria) occurred during surveillance in one case. Twelve patients (16%) underwent delayed intervention (11 surgical treatments and one ablative treatment), of which six (50%) for patient decision in the absence of treatment failure. Partial nephrectomy was possible in 90.9% of patients who underwent surgery. Eight patients carried on with AS protocol despite treatment failure. One of these patients had stage progression for the development of a tumor thrombus in the renal vein and died for metastatic disease.

TABLE I.—*Demographic and clinical characteristics of patients and renal masses.*

Variable	Whole cohort (N.=134)	AS group (N.=75)	PCA group (N.=59)	P value
Time of treatment, years	2010-2016	2010-2016	2011-2016	NA
Age, years	69.82±11.52 (31-88)	69.47±13.16 (31-87)	70.27±9.12 (45-88)	0.330
Sex				0.056
Male	93 (69.4%)	47 (62.7%)	46 (78.0%)	
Female	41 (30.6%)	28 (37.3%)	13 (22.0%)	
Side (n, %)				0.021*
Left	69 (51.5%)	32 (42.7%)	37 (62.7%)	
Right	65 (48.5%)	43 (57.3%)	22 (37.3%)	
Charlson Comorbidity Index				
0	36 (26.9%)	15 (20.0%)	21 (35.6%)	0.043*
1-3	75 (56.0%)	44(58.7%)	31 (52.5%)	0.478
>4	23 (17.2%)	16 (21.3%)	7 (11.9%)	0.149
Tumor size, mm	20.70±8.63 (5-40)	19.52±8.85 (6-40)	22.20±8.18 (5-40)	0.071
Tumor pattern				0.004*
Solid	124 (92.5%)	65 (86.7%)	59 (100%)	
Cystic	10 (7.5%)	10 (13.3%)	0 (0%)	
Biopsy				
Overall	73 (54.4%)	19 (25.3%)	54 (91.5%)	<0.001*
Diagnostic	51 (69.9%)	13 (68.4%)	38 (70.3%)	0.873
Histology at biopsy (N., %)				
RCC	41 (80.4%)	10 (76.9%)	31 (81.6%)	0.715
Oncocytoma	9 (17.7%)	3 (23.1%)	6 (15.8%)	0.552
Angiomyolipoma	1 (1.9%)	0 (0%)	1 (2.6%)	0.555
Follow-up, months	35.31±21.19 (6-111)	36.83±25.17 (6-111)	33.39±14.94 (8-62)	0.353

Continuous and categorical variables are reported as mean±SD and frequency (proportion), respectively.
*Statistically significant (P<0.05). AS: active surveillance; PCA: percutaneous cryoablation; RCC: renal cell carcinoma; NA: not applicable.

TABLE II.—*Patterns of treatment failure in patients undergoing AS and PCA.*

Variable	N. (%)
Failure in AS group (N.=14)	
Dimensional progression	14 (18.7%)
Doubling time <12 mm	11 (7.9%)
Tumor diameter >4 cm	8 (10.7%)
Stage progression	1 (1.3%)
Distant metastasis	1 (1.3%)
Onset of tumor related symptoms	1 (1.3%)
Failure in PCA group (N.=7)	
Local recurrence	6 (10.2%)
Distant metastasis	1 (1.7%)
Onset of tumor related symptoms	0 (0%)

AS: active surveillance; PCA: percutaneous cryoablation.

PCA was inadequate at early scanning in two cases (3.4%) requiring a re-ablation. In the PCA group treatment failure was observed in seven patients (11.9%) due to local recurrence. In three cases (5.1%) a repeat percutaneous ablation was performed successfully, while four patients were started on surveillance. One patient had tumor seeding along the needle track at 12 months and died within 6 months from metastatic disease with multiple thoracic and visceral metastases.

Time to treatment failure was longer, albeit not statistically significantly, in the AS cohort (25 *vs.* 12 months, P=0.647).

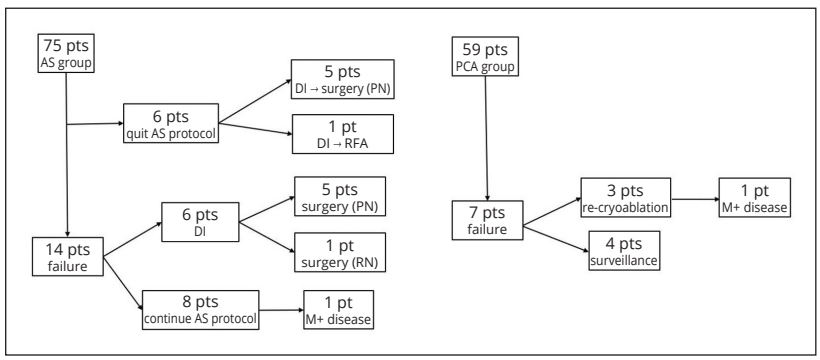

Figure 1.—Delayed treatment after failure in patients undergoing AS and PCA.
AS: active surveillance; PCA: percutaneous cryoablation; DI: delayed intervention; RFA: radiofrequency ablation; M+: metastatic disease.

No significant difference was observed for CSS in the two groups (95.8 *vs*. 98.2% at 5 years follow-up in AS and PCA patients, respectively (P=0.831). Five-year OS was higher, albeit not significantly for patients in the PCA group compared to those in the AS group (96.5% *vs*. 82.4%, P=0.113) respectively. There was no statistically significant difference in FFS among the two groups. At 2 and 5 years 90.9% and 70.1% of patients were alive without treatment failure in the AS group, while 93.1% and 70.9% were alive without treatment failure in the PCA group respectively (P=0.645). (Figure 2).

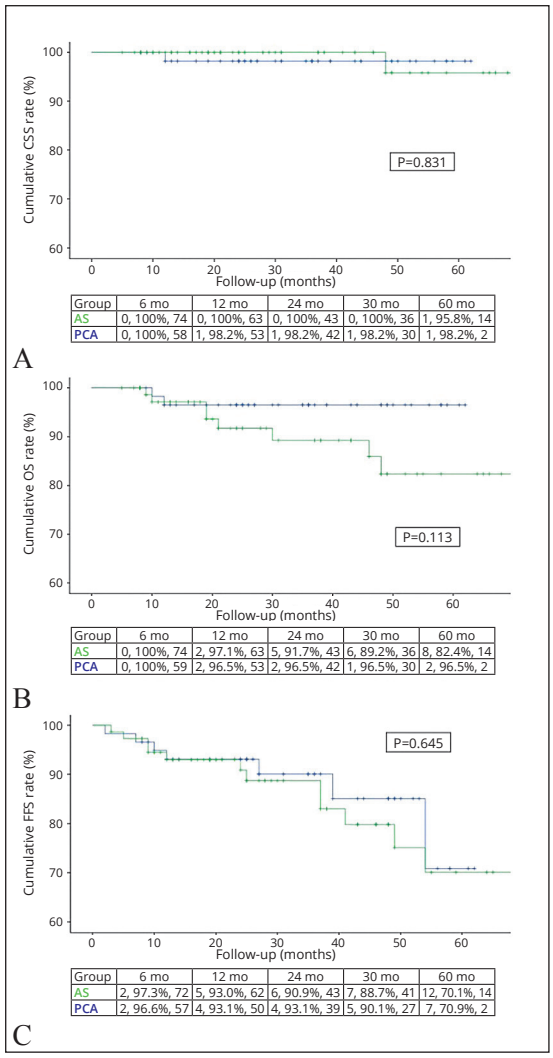

Figure 2.—Kaplan-Meier survival analysis for: A) cancer-specific survival (CSS); B) overall survival (OS); C) failure-free survival (FFS) in the group of patients undergoing AS and cryoablation.
AS: active surveillance; PCA: percutaneous cryoablation; FFS: failure-free survival; CSS: cancer specific survival; OS: overall survival.

In the PCA group the complication rate was 5% (Clavien grade 1-2) and no high-grade complication (Clavien 3-5) was observed.

Discussion

We compared the intermediate-term oncological outcomes of AS and PCA in patients with incidentally detected SRMs and we observed comparable CSS and FFS in the two cohorts of patients included in our analysis. At an average follow-up of 35 months we observed only one cancer specific death per group, one due to needle tract seeding after PCA and one due to stage progression during AS.[13] There was a non-significant trend towards better OS at 5 years for PCA.

Surgery is the gold standard treatment for small renal masses. Recent data showed that robot-assisted partial nephrectomy can be offered also to patients with very small renal masses, as it carries minimal risk of complications and has minimal impact on renal function.[14] AS and PCA are currently considered valid alternatives to surgical treatment in the management of SRMs especially in the elderly and frail population,[1-3, 15] providing excellent functional and oncological outcomes.[16]

However, the majority of available studies are single center series providing only short-term outcomes (<24 months), using non standardized follow-up protocols and lacking standardized definitions for treatment failure.[3, 17] Moreover, most studies include mainly patients with advanced age, significant comorbidities and poor performance status, leading to shorter life expectancy and high competing cause mortality. Therefore, it is difficult to assess the oncological efficacy of non-surgical approaches for SRMs based on these studies.[3]

The ideal way to evaluate the oncological value of AS and PCA would be to compare their results with those of surgical treatment in a randomized study. However, there is currently no data from randomized controlled trial comparing radical and partial nephrectomy with AS and thermal ablation.[18, 19] Researchers from UK

came to the conclusion that such randomised trials are not easily feasible for the difficulty to recruit due to a lack of equipoise on the part of clinicians and an unwillingness of patients to be randomised.[20]

In an effort to contribute to answer this clinical question we analyzed prospectively collected data from two cohorts of patients who were managed either with AS or PCA for an incidentally detected SRM. Although the treatments were performed at different institutions, the two cohorts were comparable in terms of age, tumor size and pathology. As expected, comorbidities were more significant in the AS group.

The aim of the study was to compare the oncological outcomes of PCA, a non-surgical minimally invasive procedure, with those of AS, a non-interventional treatment modality. The risk of progression to distant metastases and cancer-specific death is relatively low for SRMs.[21] For this reason we also assessed FFS since treatment failure is in our opinion a significant endpoint for non-surgical treatment modalities since it has the potential to trigger a timely delayed or salvage intervention aiming to obtain local control and potentially improve outcomes.[22]

We acknowledge that this comparison is limited by the different definitions that are used to define treatment failure and in particular local treatment failure in the two populations. In AS the definition of local treatment failure is based mainly on the growth kinetics of the SRM, while in the PCA group local treatment failure is mainly defined by the persistence or new onset of contrast enhancement in the ablated area at imaging.[17, 23-25]

With these limitations, FFS was not significantly different at 2 and 5 years between AS and PCA. The mean time to progression was significantly longer in the AS group (25 vs. 12 months), which is likely explained by the different criteria used to define treatment failure. CSS was excellent and comparable in the two cohorts with only one cancer specific event in each group. Our data confirm once again the indolent clinical behaviour of the majority of SRMs, as shown in other non-randomized comparisons between treatment modalities for small renal tumors.[9, 26] Furthermore, salvage or delayed intervention seemed to be able to rescue the majority of treatment failures. A proper use of delayed intervention when dimensional or clinical progression is detected is crucial to achieve optimal survival outcomes during AS. Very importantly, delayed nephron-sparing treatment was possible in >90% of patients who experienced treatment failure during AS, confirming the safety of this approach also from a functional point of view.

OS rates were also good in both groups at intermediate-term follow-up. The significantly higher comorbidity index of patients managed with AS is reflected in a trend towards a poorer OS in this group of patients. This difference will likely become significant in the long term.

In our series, 13% of tumors in the AS group had a cystic pattern, while all ablated tumors had a solid pattern since the role and safety of cryotherapy in the management of cystic lesions is not well defined and only a few cases have been reported to date.[27] The natural history of cystic renal tumors has been shown to be more indolent and this may represent a bias in the interpretation of the results.[28] However, most cystic tumors managed with AS in this series were Bosniak IV lesions and therefore had a higher risk of malignancy and biological aggressiveness.[29]

Obtaining information about renal tumor histology with percutaneous RTBs is recommended before tumor ablation and in selected patients considering AS.[1] According to the current guidelines the vast majority of patients (91,5%) in our study underwent a RTB before PCA, while 25% of patients underwent a RTB prior to enrolment in the AS protocol. This proportion is higher compared to the largest recently published clinical series of AS.[9] As it may be expected more than 75% of the biopsied tumors were histologically confirmed as RCCs in both treatment groups.[30]

Limitations of the study

The main drawback of this study is its retrospective and non-randomized design. Only a randomized controlled trial could provide high-level evidence to support strong statements on the oncological safety and on the best suited indications for non-surgical treatment modalities for SRMs. Nevertheless, randomization for these trials is

very challenging and a long follow-up is needed to provide robust data on CSS, based on the low proportion of cancer-specific events in this low-risk patient population. Secondly, treatment failure may not be a significant predictor of CSS since progressors may be rescued with appropriate and timely delayed or salvage intervention. Finally, as previously mentioned, our data may be biased by the definition of treatment failure, which is inevitably different when we compare an interventional with a non-interventional treatment. On the other end, the strengths of our study are represented by the consistent series of patients in the two treatment groups, who were managed with a standardized approach and followed for a follow-up period >3 years with a standardized protocol with no patients missed at follow-up.

Conclusions

Overall, our data shows that AS and PCA have similar intermediate-term survival outcomes and are valid alternatives to surgery for treatment of SRMs, particularly in patients with a significant competing cause mortality risk. Data from larger and ideally randomized studies comparing non-surgical treatment modalities for SRMs are needed to confirm these findings.

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