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ARTICLE

Renal cryoablation: five- and 10-year survival outcomes in patients with biopsy-proven renal cell carcinoma

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ABSTRACT

Objective: To investigate the long-term oncological efficacy of renal cryoablation (CA) of small renal tumors.

Materials and methods: A review of patients treated with CA for a biopsy confirmed renal cell carcinoma less than 4 cm in diameter. All patients were identified from a prospectively maintained clinical database. Treatment efficacy was computed using the Kaplan-Meier method to estimate disease-free survival (DFS) and overall survival rates (OS).

Results: A total of 179 patients (116 men and 63 women) with a mean age of 64 years (95% CI = 63 – 66) were included in the analysis. Mean tumor size was 27 mm (95% CI = 25.5–28.0) with a low, moderate and high PADUA complexity score in 30.2%, 44.7% and 16.2% of the cases, respectively. A total of 19 patients (11%) were diagnosed with residual unablated tumor, six patients (3%) were diagnosed with late local recurrence and six patients (3%) were diagnosed with metastatic disease. The estimated 5 years image confirmed the DFS rate was 79% (95% CI = 70–85). The estimated 5- and 10-year OS rates were 82% (95% CI = 75–87) and 61% (95% CI = 48–71), respectively. During the 10-year follow-up period a total of five patients (3%) died due to renal cancer, while 46 patients (26%) died from other causes.

Conclusions: CA appears to be an effective treatment modality for patients with small renal tumors. The present study demonstrated low rates of local recurrence and disease progression with excellent long-term cancer-specific survival.

Abbreviations: ASA: American Society of Anesthesiologists; AUA: American Urologic Association; CA: renal cryoablation; CT: computer tomography; DFS: Disease-free survival; EAU: European Association of Urology; ECOG: Eastern Cooperative Oncology Group; MRI: magnetic resonance imaging; OS: Overall survival; PADUA: preoperative aspects and dimensions used for anatomical classification; PCA: percutaneous CT-guided cryoablation; RCC: renal cell carcinoma; SRM: small renal masses.

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Introduction

The incidence of renal cell carcinoma (RCC) is increasing, with an estimated 3900 new cases in the Nordic countries and 1470 estimated deaths each year. However, over the past 10 years the mortality rate has been falling on average 1.5% and 2.7% for men and women, respectively [1]. The increased incidence is largely driven by the incidental detection of small renal masses found on cross-sectional imaging in relation to other causes. As a result, there has been a stage migration towards lower tumor stages at the time of presentation [2]. Treatment of localized RCC has evolved from open surgery towards minimally invasive and nephron-sparing procedures, in particular partial nephrectomy has become the preferred treatment modality for small renal masses.

Thermal ablation techniques have evolved significantly over the past two decades, with most cases now being performed as an image-guided procedure, mainly CT- or MR-guided. Recently, the American Urologic Association (AUA) advised the use of ablative therapy as an alternative treatment for tumors <3 cm in all patients and recommend it in comorbid patients who are at surgical risk [3]. The European Association of Urology (EAU) is still cautious and emphasizes the low quality of the available data as a reason for recommending thermal ablation only for elderly patients and/or patients with significant comorbidities [4]. We and others have reported favorable outcomes and low complication rates, suggesting that thermal ablation is an acceptable treatment option in selected patients [5]. This is also what has been recommended in the latest UK National Comprehensive Cancer Network kidney cancer guidelines [6].

The present study analyses the long-term treatment efficacy and survival of patients who were treated with CA of incidentally detected cT1a biopsy proven RCC.

Materials and methods

Patients selection

Prior to treatment, all patients had an ultrasound-guided 18-G core biopsy and were discussed at a local multidisciplinary

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team meeting and underwent normal outpatient urology consultation before the treatment modality was determined. The primary clinical indication for CA included contraindications to surgery, significant comorbidities and patient preferences. Patient and treatment data were prospectively recorded in a clinical database to enable subsequent determination of treatment success. Patient demographics and tumor characteristics are presented in Table 1.

Procedure

Our institution initially performed CA as a laparoscopic-assisted and ultrasound guided procedure, but in 2013 we undertook a gradual conversion to percutaneous CT-guided cryoablation (PCA). All tumors were treated with the intention of complete ablation in a single session using a double freeze–thaw cycle (10 min freeze, 8 min thaw, 10 min freeze) reaching at least −40 °C in the tumor. The laparoscopic-assisted cryoablative procedure has previously been described [7]. All cryoablative procedures were performed using the Galil Medical/BTG cryoablation system (Galil Medical, Arden Hills, Minneapolis, MN). All patients were treated under general anesthesia.

Follow-up

Treatment success was evaluated by postoperative follow-up imaging, typically adhering to a protocol of 3- and 12-months imaging, and thereafter on a yearly basis for another 4 years. Follow-up imaging comprised of contrast-enhanced CT and in some cases MRI. Treatment efficacy (no residual unablated tumor) was defined as a complete response with no residual enhancing tumor by 3 months, with the non-enhancing ablation zone more than encompassing the previous tumor. Late local recurrence was defined as any nodular or growing enhancement within the ablation zone occurring after documented adequate ablation from at least one contrast-enhanced scan. Disease-free survival (DFS) was defined as the time from cryoablative treatment until either residual unablated tumor, late local recurrence, or metastatic disease was diagnosed. Overall survival (OS) was defined as the time from treatment until the patient died of any cause or last check of survival status.

Table 1. Baseline demographics and tumor characteristics.

	Results
Age, year, mean (95% CI)	64 (63–66)
Gender, *n* (%)	
Male	116 (64.8)
Female	63 (35.2)
ASA score, *n* (%)	
I & II	91 (50.8)
III	37 (20.7)
IV	1 (0.6)
n/a	50 (27.9)
ECOG performance status, *n* (%)	
Grade 0 & I	86 (48.0)
Grade II	42 (23.5)
Grade III	1 (0.6)
n/a	50 (27.9)
Charlson comorbidity index, *n* (%)	
0–3	100 (55.9)
4–5	36 (20.1)
6–7	12 (6.7)
>7	11 (6.1)
n/a	20 (11.2)
Serum creatinine, μmol/L, mean (95% CI)	92 (83.9–99.9)
Tumor size, mm, *n* (%)	
<20 mm	33 (18.4)
21–30 mm	71 (39.7)
>30 mm	75 (41.9)
PADUA complexity score, *n* (%)	
Low	54 (30.2)
Moderate	80 (44.7)
High	29 (16.2)
n/a	16 (8.9)
Biopsy findings, *n* (%)	
RCC, clear cell	119 (66.5)
RCC, papillary type 1	11 (6.1)
RCC, papillary type 2	10 (5.6)
RCC, papillary, subtype unknown	15 (8.4)
RCC, chromophobe	11 (6.1)
RCC with subtype unknown	13 (7.3)

Statistical analysis

Statistical analyses were performed according to a predefined statistical analysis plan. DFS and OS were estimated using the Kaplan–Meier method. Duration of DFS follow-up was calculated from the time of treatment to the time of image confirmed residual unablated tumor, late local recurrence, metastatic disease, or last known imaging status. Duration of OS follow-up was calculated from the time of treatment to death or date of last survival-status-check of the patient. Due to the very limited number of cancer-related deaths we refrained from cancer-specific survival analyses. Data analyses were conducted using STATA v.14 software (StataCorp, LP, Lakeway, Texas, USA).

Results

A total of 184 patients with a biopsy confirmed tumor were treated between 2005 and 2014. Five patients were lost to follow-up, thus not included in the analysis, leaving the study cohort as 179 patients (116 men and 63 women) with a mean age of 64 years (95% CI = 63 − 66). The distribution with respect to the ASA classification system was: ASA I & II (50.8%), ASA III (20.7%), and ASA IV (0.6%). The distribution of the ECOG Performance Status was: Grade 0 or 1 (48.0%), Grade 2 (23.5%) and Grade 3 (0.6%). The mean Charlson Comorbidity Index was 3.5 (95% CI = 3.3–3.8). The mean pre-treatment s-creatinine level was 92 μmol/L (95% CI = 83.9–99.9). The mean tumor size on cross-sectional imaging was 27 mm (95% CI = 25.5–28.0) with size distribution being <20 mm in 33 cases (18%), 21–30 mm in 71 cases (40%) and >30 mm in 75 cases (42%). The PADUA anatomical tumor complexity score was Low (6–7) in 30.2%, Moderate (8–9) in 44.7% and High (10–12) in 16.2% of the cases. Tumor histology consisted of the following subtypes: clear cell (66.5%), papillary type 1 (6.1%), papillary type 2 (5.6%), papillary subtype unknown (8.4%), chromophobe (6.1%), and RCC subtype unknown (7.3%).

A total of 19 patients (11%) were diagnosed with residual unablated tumor, six patients (3%) were diagnosed with late local recurrence and six patients (3%) were diagnosed with metastatic disease (biopsy confirmed). The majority of cases

Table 2. Tumor and salvage details following treatment failure of initial cryoablation.

Age (gender)	Tumor size (mm)	PADUA	Renal cell cancer subtype	Cause of treatment failure	Salvage treatment	Current follow-up status*
71 (f)	30	High	Chromophobe	Residual tumor	Reablation	Alive
60 (f)	26	Moderate	Clear cell	Residual tumor	Reablation	Alive
69 (f)	24	Moderate	Clear cell	Residual tumor	Reablation	Alive
68 (m)	22	Moderate	Clear cell	Residual tumor	Reablation	Alive
54 (m)	30	Low	Clear cell	Residual tumor	Reablation	Alive
49 (m)	30	High	Clear cell	Residual tumor	Reablation	Alive
82 (f)	37	Moderate	Clear cell	Residual tumor	Reablation	Alive
70 (m)	40	High	Clear cell	Residual tumor	Reablation	Alive
67 (m)	25	High	Clear cell	Residual tumor	Reablation	Alive
42 (f)	30	Moderate	Clear cell	Residual tumor	Reablation	Alive
54 (m)	30	Moderate	Clear cell	Residual tumor	Partial nephrectomy	Alive
82 (f)	34	Moderate	Clear cell	Residual tumor	Partial nephrectomy	Alive
54 (m)	40	Moderate	Clear cell	Residual tumor	Nephrectomy	Alive
72 (m)	42	High	Clear cell	Residual tumor	Nephrectomy	Alive
79 (m)	39	High	RCC, subtype n.a.	Residual tumor	Reablation	Dead, other cause
73 (m)	28	Low	Clear cell	Residual tumor	Reablation	Dead, other cause
60 (m)	40	Moderate	Clear cell	Residual tumor	Reablation	Dead, other cause
67 (m)	20	Moderate	Clear cell	Residual tumor	Reablation	Dead, other cause
75 (m)	42	High	Clear cell	Residual tumor	Active surveillance	Dead, other cause
56 (f)	25	Moderate	Clear cell	Local recurrence	Reablation	Alive
65 (m)	31	Moderate	Clear cell	Local recurrence	Reablation	Alive
71 (f)	33	Moderate	Clear cell	Local recurrence	Partial nephrectomy	Alive
68 (f)	38	High	Clear cell	Local recurrence	Nephrectomy	Alive
80 (m)	23	High	Papillary, type 2	Local recurrence	Nephrectomy	Dead, other cause
71 (m)[a]	43	Moderate	Clear cell	Local recurrence	Oncology	Dead, cancer specific
55 (m)	26	Moderate	Clear cell	Metastatic (bone)	Oncology	Alive
61 (f)	22	Moderate	Papillary, subtype n.a.	Metastatic (lung)	Oncology	Alive
78 (m)	25	High	Papillary, subtype n.a.	Metastatic (liver)	Oncology	Dead, cancer specific
77 (m)[b]	23	Low	Clear cell	Metastatic (bone)	Oncology	Dead, cancer specific
69 (m)[c]	25	Low	Clear cell	Metastatic (lung)	Other surgery	Dead, cancer specific
71 (f)	41	High	Clear cell	Metastatic (lung)	Other surgery	Dead, cancer specific

*Current follow-up status portrays the last know vital status of the patient (December 2019).
[a]Damage to the ureter during treatment. Local recurrence is diagnosed 12 months after treatment. General condition is to poor for surgical treatment.
[b]Bone metastasis was diagnosed only 6 months after treatment.
[c]Underwent nephrectomy at the same time as cryoablation due to bilateral tumor.
n.a., not applicable.

with residual unablated tumor and late local recurrence were salvaged with re-ablation and none of these patients died due to renal cell cancer. Only one patient who developed local recurrence and later also metastatic disease died due to cancer specific causes (Table 2). The Kaplan-Meier estimates of 3- and 5-year images confirmed DFS rates were 85% (95% CI = 78–89) and 79% (95% CI = 70–85), respectively (Figure 1). The Kaplan-Meier estimates of 5- and 10-year OS rates were 82% (95% CI = 75–87) and 61% (95% CI = 48–71), respectively (Figure 2). A total of five patients (3%) died of renal cell cancer, while 46 patients (26%) died of other causes. One of the patients who died of RCC had undergone radical nephrectomy at the same time as CA due to bilateral disease.

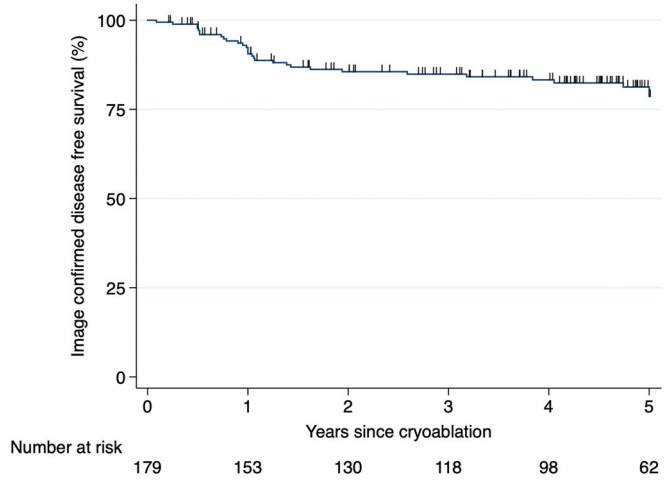

Figure 1. Kaplan-Meier plot depicting disease-free survival.

Discussion

When treating small renal masses (SRMs), cancer control, preservation of renal function and patient comorbidity should be balanced. The clinical management of incidental detected SRMs has gradually changed from radical extirpative surgery to minimally invasive treatment options and remains finely balanced between surgery, ablation and active surveillance [8]. The gold standard for the treatment of SRMs remains surgical resection, preferably as partial nephrectomy. However, ablative modalities are becoming increasingly more common in the management of these tumors. Moreover, it is important to recognize that many of these patients, due to age, carry significant competing risks which potentially pose a greater mortality risk than the SRM itself [9,10]. The short- and medium-term efficacy of CA have been presented in a broad range of single and multi-institutional studies, but rarely with long-term follow-up, and none in a Scandinavian setting.

The present study has demonstrated that CA delivers long-term overall survival results that are on par with what is known from surgical resection and that cancer-specific death among these patients are rare. In 2015, Thompson et al. [11]

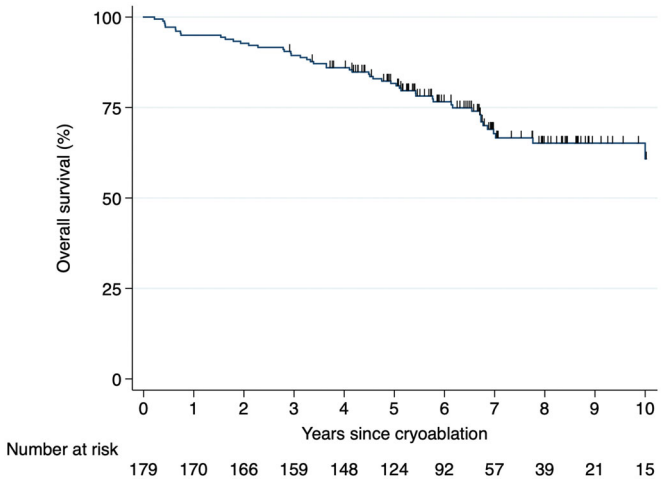

Figure 2. Kaplan-Meier plot depicting overall survival.

published a large series from the Cleveland Clinic, comparing partial nephrectomy with ablation, and found that recurrence- and metastases-free survival were similar. In another study comparing nephron-sparing surgeries and ablation, Whitson et al. [12] demonstrated that 5-year disease-specific survival was similar between the two groups. In a large multicenter study of patients having undergone laparoscopic-assisted CA, we previously reported a 5-years disease-specific and overall survival rate of 90.4% and 83.2%, respectively [5]. The DFS rate found in this study is lower than what is generally reported for partial nephrectomy and may in part be explained by the initial learning curve subsequent to CA introduction. Also, the technical failures (residual unablated tumors) are included in the DFS-rate, but most of these patients underwent a second cryoablative procedure and continued follow-up without any event. If the technical failures salvaged by a second ablative procedure were to be considered non-failures the 5-years DFS would increase from 79% to 85%. Furthermore, not all failures were biopsy confirmed prior to salvage treatment, thus a risk of false-positive failures exists.

CA was in many centers initially introduced as a laparoscopic-assisted procedure but has gradually changed into becoming an interventional procedure performed by radiologists, and in most centers as a PCA procedure. One major challenge when performing laparoscopic-assisted CA was the ability to monitor the deep margins of the iceball as intraabdominal ultrasound images are blocked by the formation of the iceball. With real-time cross-sectional imaging CA has evolved considerably and offers good control over the ablation zone. In 2018, Breen et al. [13] published a series of 220 patients treated with PCA for biopsy-proven RCC and reported a 5-year local recurrence free survival rate of 93.9%, a metastasis-free survival rate of 94.4% and an overall survival rate of 78.8%.

To ensure successful treatment and reduce the risk of serious complications, correct patient selection is crucial. In early experience tumor complexity, including some polar and hilar locations, played a role in tumor selection for the modality. But with increasing experience and the use of fluid or gas infusion under image guidance to displace adjacent viscera most SRM's can now be treated using PCA. Endophytic tumors with proximity to the renal collecting system are not considered an absolute contraindication, but awareness of the relative warming of the ablation zone by large central vessels is important as more aggressive freezing may be necessary to achieve cryocidal temperatures. In rare cases we have experienced obstruction of renal calyces in relation to treatment of very central tumors. Close attention must be paid to lower pole tumors with close proximity to the ureter, and often we avoid treating these tumors with CA due to the risk of damage to the proximal ureter (urothelial stricture). In general, CA represents an attractive treatment option for patients with von Hippel-Lindau or other inheritable renal tumors owing to the multifocal recurrent nature of their disease. Other indication for CA may include patients with a solitary or transplanted kidney and also recurrence after previous ablation or PN are potential indications for CA. The minimally invasive nature and maximal preservation of renal function are the main advantages of CA.

Safety and efficacy are well reported in the literature, but follow-up protocols are ill-defined, and the major urological guidelines (AUA/EAU) provide only limited guidance. Follow-up after ablative treatment aims at two things; one is to confirm technical incomplete ablation (residual unablated tumors) as early as possible and the second is to diagnose the development of local recurrence or metastatic disease. In 2016 an international multidisciplinary Delphi consensus project published its follow-up recommendations and suggested: First imaging at 3 months post-treatment. Minimum follow-up of 5 year but preferably extended to 10 years. Biannual imaging in the second year. Annual imaging from the third year onwards. First option should be 3-phase CT and second option MRI with multiparametric protocol [14].

The present study did not perform complication analysis as this was outside the aim of this study. We have previously presented such data for an at large multinational cohort of patients treated with laparoscopic-assisted CA and found that severe complications (Clavien-Dindo grade $\geq$ III) were observed in 3.2% of the cases [5]. In a recently presented study of 433 patients treated with PCA the rate of severe complication was found to be 4.9% [13]. Furthermore, a large study on renal function loss following CA in single kidney patients found that treatment resulted in an eGFR of only -3.1 ml/min/1.73 m^2 [15]. We refrained from performing multivariant analysis in the present study owing to the limited number of patients and relatively few events. It has previously been demonstrated how tumor size and PADUA-score as categorical variable were able to predict treatment outcome [5,7].

The main advantage to this study is the meticulous long-term follow-up of this biopsy confirmed cohort of patients with SRMs. Analysing the early laparoscopic data offers an ability to gain important knowledge about the long-term outcomes of patients treated with CA. But the study also has some notable limitations despite being based on a prospectively maintained database. First, the results require interpretation in the light of their single-center and non-randomized nature, thus selection bias and residual confounding are

likely. Second, treatment protocols and especially follow-up protocols have varied slightly during the study period. Also, we did not have biopsy confirmatory data on all failure cases, thus some cases could potentially have been false positives. Furthermore, as the data also encompass the early period of CA a certain degree of learning curve are likely to be reflected in data, especially with respect to residual tumors. Finally, owing to the slow-growing nature of SRMs, a longer follow-up period with late cross-sectional imaging would have allowed for additional accruement of potential failure cases.

In conclusion, CA appears to be an effective treatment modality for patients with small renal tumors. The present study demonstrated low rates of local recurrence and disease progression with excellent long-term cancer-specific survival.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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