

Percutaneous cryoablation and (partial) nephrectomy of small renal tumors

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Abstract

Background- In the Netherlands 2700 patients get diagnosed with renal cancer yearly, the typical age is 50-70 years old. The 5-year overall survival for T1(≤ 7 cm) renal carcinoma equals 88%. Amongst treatment options, percutaneous cryoablation(PCA) is associated with less complications and (partial) nephrectomy with better oncologic outcomes.

Methods- Between august 2015 and august 2022 all patients that received primary treatment for a small renal tumor(≤ 4 cm) were included. For the PCA group, repeat interventions were necessary in some cases, those interventions have been included in the analysis of the perioperative complications (CDC < 30 days). Oncologic outcomes have been analyzed for patients in follow-up; OS up to 5-years, local and distant recurrence rate.

Results- Total of 455 patients were included, 311 (P)N and 134 in the PCA group. The same number of (P)N's resulted in 6,4% procedural and 24,8% post-procedural complications. Local and distant recurrence was 1,7% for both and 6 patients in the follow-up are reported dead, none caused by renal cancer. 154 PCA's were performed, 3,9% procedural and 5,8% post-procedural complications. These patients showed 8,3% local and 6,4% distant recurrence, when correcting for confirmed malignancy this was 9,0% and 10,4%. A total of 9 deaths were reported, 6 in the confirmed group, 3 caused by renal cancer.

Conclusion- The patient selection shows that PCA is performed on older and less healthy patients and with less complications than the (P)N group. Survival for both groups was high with the oncologic outcomes favoring (P)N. These results are in accordance with literature.

Background

Annually about 2700 patients get diagnosed with a form of renal cancer in the Netherlands, this accounts for 2% of all types of cancers. Typical age of diagnosis is 50-70 years old, but incidence increases with age, it has a male to female ratio of 2:1.(1,2,3) The worldwide estimation, done in 2020, ranges somewhere around 300,000 new diagnoses per year.(4,5) About 20% of small renal tumors found are benign, meaning 80% are malignant.(6) The majority, 90-95%, of renal carcinomas are classified as renal cell carcinoma(RCC), with urothelial cancer and Wilms tumor making up the remaining minority of cases.(7,8,9) The incidence of renal masses and renal cancer has been rising over the last decades, this is due to the increasing quality and number of imaging techniques, now there is computed tomography(CT), magnetic resonance imaging(MRI) and the use of the ultrasound with different modalities.(10,11,12) Usually the tumor is found by accident, an incidentaloma, in

most cases the patient is asymptomatic and the tumor is in a low stage of malignancy.(13,14,15)

The 5-year survival constitutes 66% when including all stages of disease and yearly 900 deaths are reported, in the Netherlands. Most diagnoses however, are in the first stage of disease with a 5-year survival rate of 88%. This study is aimed at patients with stage 1(T1) diagnosis that have a renal tumor smaller than 4 centimeters (T1a). (1) Risk of metastasis is low, a Korean study with 1913 patients with a small renal mass had a risk of distant recurrence after (partial) nephrectomy ranging from 1,1% to 6,0%. The bigger the size of the tumor was, the higher the chance for a distant recurrence of the tumor.(16)

An Italian study found the three-year overall survival after PCA to be 80% and a recurrence free survival of 91%.(17)

There are a number of treatment options for these smaller tumors: Focal ablation, radiotherapy, (partial) nephrectomy and no active treatment also called active surveillance(18). Nephron-sparing procedures have become more preferable over more radical approaches in treating renal carcinoma.(19,20) Active surveillance has also been an increasing approach to managing renal masses.(21) This due to the preservation of kidney function, percutaneous cryoablation and partial nephrectomy are such procedures. This study focuses on the patient characteristics and oncologic outcomes of cryoablation and (partial) nephrectomy performed in a high volume renal-cancer center as well as perioperative complications. Percutaneous cryoablation(PCA) is regarded as a non-invasive treatment with a lower chance of complications. (Partial) nephrectomy((P)N) is considered an invasive form of surgery with a high success rate regarding the oncologic outcomes, but with a higher chance of complications. (22,23,24)

Research question: What are the patient and tumor characteristics, rate of complications and oncologic outcomes when small renal tumors are treated by (partial) nephrectomy or percutaneous cryo-ablation?

Method

Retrospectively all patients with a small renal tumor (T1a) were evaluated who underwent a percutaneous cryoablation(PCA) or (partial) nephrectomy between august 2015 and august 2022 , in a single Dutch high volume renal cancer center, st Antonius hospital in Nieuwegein. The patient and tumor characteristics including kidney function, aspects of the procedure, complications during the procedure and 30 days after the procedure rated according to the Clavien-Dindo classification (CDC <30 days) will be extracted from the electronic patient records.

The age of the patient is determined on the day of the procedure and the ASA-classification(American society of anesthesiologists) is defined by a certified anesthesiologist during the pre-operative screening. The kidney function is determined before the procedure which is protocol for any surgery and, if available, the kidney function after a year is extracted from the electronic patient records.

All procedures, including repeat interventions following the initial treatment, are taken into account in discerning the complications in both treatment groups, this includes the repeat

PCA's. The residual tumor after a PCA is determined after 4-6 months, imaging is performed to confirm a residual tumor, if this is not the case, the PCA was successful in removing all of the tumor. If at a later stage in the follow-up a lesion is seen at the location of the removed tumor, this is reported as a local recurrence.

In case of PCA there are cases where there is no malignant or benign tumor found in the biopsy or there is no biopsy performed, due to the difficulty in accessibility of the tumor for biopsy. This group is also followed-up by a urologist and therefore included in the follow-up of this study, along with the group of patients that have a proven malignant tumor. The entire group will thus be monitored for the years following the procedure, the kidney function after one year and oncologic outcomes will be extracted. The oncologic outcomes are described with the following variables: 5-year overall survival(OS), local and distant recurrence rate, in case of mortality, the time since the operation will be documented.

All the previously mentioned variables will be extracted from the patient records. These findings were analyzed using SPSS, for the baseline table frequencies and mean with standard deviation were used to make sure all patients would be included, procedural and post-procedural complications will also be portrayed by showing the frequency, per CDC grade for the post-procedural complications. The oncologic outcomes are analyzed and presented by dividing the patients in groups, based on how long they have been monitored in the follow-up in years. The portion of the patients surviving per group is shown in the table 4, these groups are split up in the number of full years since the procedure, up until 5 years. To display the survival over time and per distinct group according to their time in follow-up, a Kaplan-Meier curve will be constructed. The PCA patients in follow-up have either a confirmed malignancy or non-confirmed benign tumor, the latter group might consist of benign tumors, affecting the oncologic outcomes. So besides the analysis of the whole group in follow-up, a sub-analysis of the group of patients with a confirmed malignancy will be performed, concerning the oncologic outcomes and kidney function, creating a clear view of the long term results of patients treated for renal cancer.

Table 1. Baseline table, patient and tumor characteristics, kidney function

Variables	Percutaneous cryoablation (N=134)	(Partial) Nephrectomy (N=311)
Patient characteristics:		
Mean age(years) ±std	67,59 ± 10,4	59,9 ± 9,9
Sex:		
Male	100 (74,6%)	203 (65,3%)
Female	34 (25,4%)	108 (34,7%)
ASA score:		
1	6 (4,5%)	44 (14,1%)
2	70 (52,2%)	213 (68,5%)
3	54 (40,3%)	53 (17%)
4	2 (1,5%)	1 (0,4%)
Tumor characteristics:		
Mean max diameter(cm) ±std highest/lowest	2,523 ± 0,87	2,502 ± 0,8744
Pathological assessment performed	115 (85,86%)	100%
Subtyping tumor:		
Malignant		
- Clear cell renal	46 (40,4%)	180 (57,9%)
- Clear cell papillary	1 (0,9%)	5 (1,6%)
- Chromophobe		15 (4,8%)
- Papillary	23 (20,2%)	57 (18,3%)
- Multilocular cystic renal cell		7 (2,3%)
- Thyroid-like follicular		1 (0,3%)
- Acquired cystic disease-associated		1 (0,3%)
- Renal cell carcinoma undefined	1 (0,9%)	
Benign		
- Oncocytoma	12 (10,5%)	27 (8%)
- Cyste		8 (2,6%)
- Angiomyolipoma	1 (0,9%)	6 (1,9%)
- Hemangioma		1 (0,3%)
- Papilloma		1 (0,3%)
- Papillary adenoma		2 (0,6%)
- benign mixed epithelial stromal		1 (0,3%)
-Metanephric adenoma	1 (0,9%)	
-Degenerative aspects	2 (1,8%)	
-Interstitial nephritis	1 (0,9%)	
-No malignancy/pathology found	23 (20,2%)	
-Insufficient sample	3 (2,6%)	
Pathology/biopsy acquired :		
-Before intervention	63 (47%)	51 (16,4%)
-During intervention	71 (53%)	260 (83,6%)
Surgical margin +/-	N/A	Negative: 267 (85,9%) Positive: 43 (13,8%) Missing: 1(0,3%)
Location		
Left	63 (47%)	159 (51,1%)
Right	71 (53%)	152 (48,9%)
Mean kidney function (eGFR CKD-EPI) ± std pre-procedure:	61,55 ± 19,9 (N=129) Missing: 5	76,47 ± 15,5 (N=311)
<30	8 (6,2%)	
<60	53 (45%)	10 (3,2%)
		45(14,5%)

Std= Standard deviation; ASA= American Society of Anesthesiologists

Results

(Partial) Nephrectomy

Patient and tumor characteristics

The average age of patients that underwent a (partial) nephrectomy, at the time of the procedure, was $59,9 \pm 9,9$ years. Of the 311 patients, 65,3% was male and 34,7% female. The ASA-classification (American society of anesthesiologists) was distributed as follows per grade: 1 (14,1%), 2 (68,5%), 3 (17%), 4 (0,4%) and 5 (0%). In all cases the pathologist was able to perform the subtyping of the tumor, 86% of the tumors were found to be malignant, 14% were benign. A more detailed breakdown of the various subtype distribution can be found in the baseline table (table 1) as well as the tumor diameter.

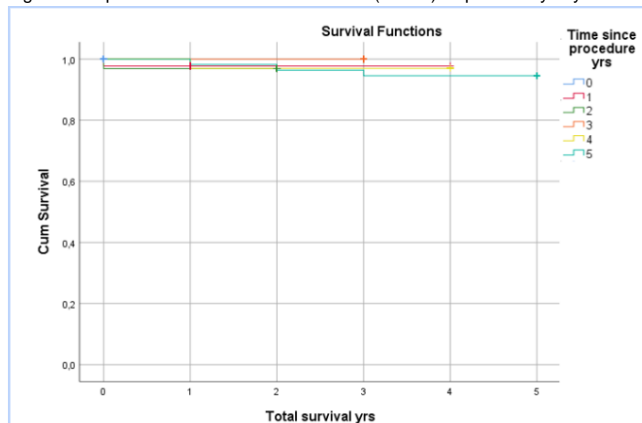
Complications during and post-procedure

The (P)N group consists of 311 patients and procedures, resulting in a 6,4% rate in procedural complications. There was a 23,3% rate for minor post-procedural complications (CDC grade 1 and 2), and 1,6% rate for major complications (CDC grade 3 and above), there was a 1,9% readmission rate within 30 days of the surgery. A more detailed display of these results can be found in table 3.

Follow-up

The number of patients in follow-up is 241. The local and distant recurrence rate is in both regards 1,7% (N=4). The 5-year OS is 94,5%, the other follow-up ranges are displayed in table 4 and a Kaplan-Meier curve (figure 1) shows the survival over time and per follow-up range. Kidney function (eGFR CKD-EPI) is on average $76,02 \pm 18,5$ at the time of treatment and after a year, $65,75 \pm 21,9$.

Figure 1. Kaplan-Meier curve. Overall survival (Partial) Nephrectomy in years



Cryoablation

Patient and tumor characteristics

The average age of patients that underwent a primary PCA at the time of the procedure was $67,59 \pm 10,4$ years. Of the 134 patients, 74,6% was male and 25,4% female. The ASA-classification (American society of anesthesiologists) was distributed as follows per grade: 1 (4,5%), 2 (52,2%), 3 (40,3%), 4 (1,5%) and 5 (0%). In 115 (85,86%) of cases a biopsy of the tumor was performed, out of these biopsies the pathologist found 62,4% of the tumors to be malignant, 15% benign and in 22,8% there was no malignancy found or the sample was deemed insufficient. A more detailed breakdown of the various subtype distribution can be found in the baseline table (table 1) as well as the tumor diameter.

Complications during and post-procedure

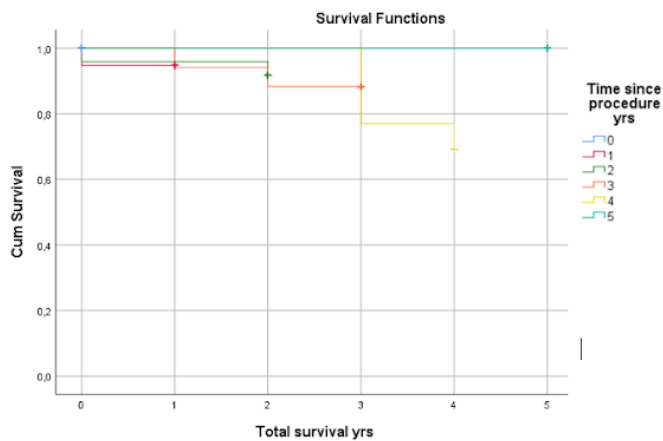
Among the total number of primary interventions ($N=134$), 9,7% ($N=15$) needed re-cryoablation, 3,2% ($N=5$) re-re-cryoablation and 0,6% ($N=1$) re-re-re-cryoablation of the primary tumor or local recurrence, totaling 154 procedures. These procedures resulted in a 3,9% rate of procedural complications. There was a 3,8% rate for minor post-procedural complications (CD grade 1 and 2), and 1,9% rate for major complications (CD grade 3 and above), only 1 (0,6%) readmission within 30 days was reported. A more detailed display of these results can be found in table 3. Residual tumor after the procedure was seen in 18,9% of cases that were eligible for a follow-up CT-scan within 4-6 months of the intervention, there were 11 patients ineligible and were thus not included in this calculation.

Follow-up

The number of patients in follow-up amounts to 109, combining patients with a proven or unconfirmed malignancy. The local and distant recurrence rate was 7,9% and 6,4% respectively. The 5 year OS is 100%, the other follow-up ranges are displayed in table 4 and a Kaplan-Meier curve (figure 2) shows the survival over time and per follow-up range. Mean kidney function (eGFR CKD-EPI) at the time of cryoablation was $60,68 \pm 20,1$ and after one year $54,24 \pm 22,0$.

Met opmerkingen [h1]: Welke graad? Voorstel: geef % 3 en hoger aan

Figure 2. Kaplan-Meier curve. Overall survival Cryo-ablation in years, malignant and unconfirmed



A total of 67 patients had a confirmed malignancy, 9,0% and 10,4% were diagnosed with a local and distant recurrence respectively. The 5-year OS is 100%, the other follow-up ranges are displayed in table 4 and a Kaplan-Meier curve (figure 3) shows the survival over time and per follow-up range. Mean kidney function (eGFR CKD-EPI) at the time of cryoablation was $58,38 \pm 20,8$ and after one year $51,30 \pm 22,4$.

Figure 3. Kaplan-Meier curve. Overall survival Cryo-ablation in years, malignant

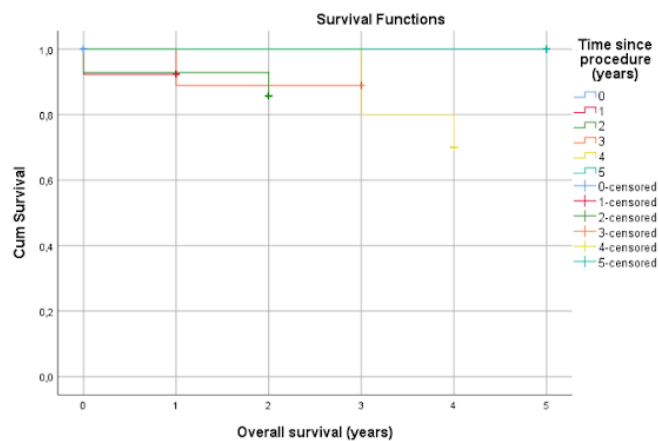


Table 2. Procedure aspects, admission time

	PCA N=154	(P)N N=311
Procedure:		
Nephrectomy =>Partial - Robot-assisted - Laparoscopic	N/A	270 (86,8%) 1 (0,3%)
=>Radical - Robot assisted - Laparoscopic - Open		2 (0,6%) 35 (11,3%) 3 (1%)
Re-cryoablation	15 (9,7%)	N/A
Re-re-cryo	5 (3,2%)	N/A
Re-re-re cryo	1 (0,6%)	N/A
Cryoablation of local recurrence	5 (3,2%)	N/A
Mean duration(min) ± std	116,97 ± 25,13 (8 missing, local no monitoring)	193,3 ± 64,05
General anesthesia during procedure	145 (94,2%)	311 (100%)
Mean Number of needles ±std	2,36 ± 1,25	N/A
Outpatient admission	67 (43,5%)	0
Mean inpatient admission duration(days) ±std	1,299 days ± 1,365	3,83 days ± 2,499
Number of days admitted: 0 (outpatient)	67 (43,5%)	
1	76 (49,4%)	23 (7,4%)
2	7 (4,5%)	91 (29,3%)
3	2 (1,3%)	82 (26,4%)
4	1 (0,6%)	45 (14,5%)
5		19 (6,1%)
6		20 (6,4%)
7		13 (4,2%)
8		8 (2,6%)
9		2 (0,6%)
10		2 (0,6%)
11		1 (0,3%)
12		12 (0,6%)
13	1 (0,6%)	2 (0,6%)
28		1(0,3%)

PCA= Percutaneous Cryo-ablation; (P)N= (Partial) Nephrectomy;

Table 3. Complications during and post-procedure, residual tumor

Number of procedures	Percutaneous cryoablation (N=154)	(Partial)Nephrectomy (N=311)
Rate of complications during procedures	6 (3,9%)	20 (6,4%)
Post-procedural complications <30days (Clavien Dindo):		
• 0 (no complication)	145 (94,2%)	234(75,2%)
• 1	3 (1,9%)	13(4,2%)
• 2	3 (1,9%)	59(19%)
• 3	2 (1,3%)	3(1%)
• 4	N/A	2(0,6%)
• 5	1 (0,6%)	
Readmission <30days	1 (0,6%)	6(1,9%)
Residual tumor (first imaging post-therapy)	27 (18,9%) Missing 11 due to term	N/A

Table 4. Oncologic outcomes

	Percutaneous cryo-ablation (Malignant+unconfirmed) N=109	Percutaneous cryo-ablation (Confirmed malignant) N=67	(Partial)Nephrectomy N=241
Oncologic outcomes:			
Local recurrence rate	8,3% (N=9)	9,0% (N=6)	1,7% (N=4)
Mean time to recurrence(Months) ±std	25,33 ± 15,24	20,83 ± 12,0	30,25 ± 11,5
Distant recurrence rate	6,4% (N=7)	10,4% (N=7)	1,7% (N=4)
Overall survival (time since procedure)			
• 0-1yr	20/20 (100%)	9/9 (100%)	48/48 (100%)
• 1-2yr	18/19 (94,7%)	12/13 (92,3%)	43/44 (97,7%)
• 2-3yr	22/24 (91,7%)	12/14 (85,7%)	31/32 (96,9%)
• 3-4yr	15/17 (88,2%)	8/9 (88,9%)	29/29 (100%)
• 4-5yr	9/13 (69,2%)	7/10 (70%)	32/33 (97%)
• 5 yr	16/16 (100%)	12/12 (100%)	52/55 (94,5%)
Mean kidney function (eGFR CKD- EPI) ±std:			
- 0yr	60,68 ±20,1 (N=105)	58,38 ±20,8 (N=64)	76,02 ±18,5 (N=241)
- 1yr	54,24 ±22,0 (N=67)	51,30 ±22,4 (N=47)	65,75 ±21,9(N=157)

Yr=year

Discussion

This study is a retrospective study describing two possible treatment options for small renal masses, performed in a single center. Both groups are of significant but different size, with the baseline table and perioperative complications accurately reported, OS has been documented and sorted per year in follow-up to give a complete overview. The findings of this study can be used and reviewed by the local urologists and intervention-radiologists that perform these procedures as a way to evaluate their patients and patients care. This study included all performed initial renal procedure and if necessary the repeat procedure within the assigned timeframe. Hence these findings show the patient and tumor characteristics, perioperative complications and overall survival of all their treated patients with a T1a renal tumor, malignant or unconfirmed histologic subtyping. The decision of which treatment was most suitable or preferable, was decided for every patient individually at that time. This was done in the form of a multidisciplinary consultation to determine the best treatment from the medical perspective and shared decision-making. The decision is made based upon the advice given by the multidisciplinary consultation team and after a conversation with the patient where this advice is discussed.

The baseline table (table 1) shows a difference in patients selected per treatment, the cryoablation group is older and, according to the ASA classification, in a worse condition overall. This is based on the invasiveness of the (partial) nephrectomy and the less invasive aspect of the percutaneous cryoablation (PCA). (22,23,24) If the two groups were to be compared correctly and with a low risk of bias, a randomized controlled trial should be set up where the patient with a small kidney tumor will be blindly allocated a random treatment.

Procedural complications were uncommon (table 3), in the PCA group the most common complication was a pneumothorax and in the (P)N group it was blood loss over 500cc. Postprocedural complications were relatively common in the (P)N group, mostly in the form of a fever, hence antibiotics were given. A review by Salargierski et al found similar outcomes in their study when looking at perioperative complications. (25) However the severe complications, class 3 till 5 according to the Clavien-Dindo classification, for both groups remained low and similar when comparing the two groups, CA 1,9% and (P)N 1,6%. Class 2 post-procedural complications seemed to be most prevalent in the (P)N group, 19,8% compared to 1,9% in the PCA group, these complications were almost exclusively a fever treated with antibiotics or blood loss supplemented with packed cells. The cryoablation wasn't always successful, resulting in a 18,7% residual rate, keeping in mind that 11 patients weren't within the range of confirming a residual tumor following the cryoablation. The success rate could also be an aspect worth considering when counseling a patient.

The (P)N group had a longer admission time (table 2), most likely because of the invasiveness of the procedure. A significant portion of the PCA group is treated in outpatient admission, the rest of the group usually stays overnight because of the time the procedure is performed. This combined with the lower number of complications, might result in a more cost-effective treatment option. In 2021 a study was published, comparing the cost-effectiveness between PCA and RAPN in treating T1a renal masses. It was concluded that PCA was the most cost-effective option, due to the lower cost of the procedure itself and the lower number of complications. (26)

The (P)N group shows a lower local and distant recurrence rate compared to the PCA group (table 4). Local recurrence does not seem to be affected by a positive surgical margin in the (P)N group, 1 in 4 cases of recurrence had a positive surgical margin. Klatte et al. performed a systematic review, similar outcomes were found concerning the local and distant recurrence rates. (23) However this study compared laparoscopic cryoablation and laparoscopic partial nephrectomy which is not entirely presentable for the population of this study. Lee H et al. deemed the size of the tumor to be indicative of the metastatic potential, in their assessment the tumors above 2 centimeters had more distant recurrences than the tumors under 2 centimeters. (16) Daugherty et al. concluded that size along with histologic subtyping and clinical staging could be key in counseling and managing small renal masses. Clear cell subtyping had the highest metastatic potential. (27)

Survival in both groups was high, in overall survival and cancer-specific survival, this is in line with the literature. (28,29) Among the (P)N population, six cases of death occurred, none caused by renal cancer. The PCA group 9 patients died, 3 deaths caused by renal cancer including metastasis of the primary tumor. When analyzing the group with a confirmed

malignancy, the recurrence numbers increase and 7 people are reported dead, of which 3 caused by metastatic progression of the malignancy. Still giving both treatment groups a high cancer specific survival. The oncologic outcomes of this study haven't been corrected for age, comorbidities or other patient and tumor characteristics. There might be a difference in cancer-specific survival based on tumor size favoring smaller tumor sizes.(30) Active surveillance has been increasingly popular as a way of managing small renal masses, Tang et al. concluded that tumor progression and a tumor size above 2 cm were related to a worse prognosis regarding overall survival.(31) One patient of the PCA group was pronounced dead 20 days after the procedure, no cause of death has been documented. Azevedo et al performed PCA on 71 patients and found comparable results in survival, deeming it similar to PN but with less major complications. (21)

A limitation regarding the recurrence and survival rate is caused by a portion of the patients that have not had a biopsy or an inconclusive result. Hence the group with a confirmed malignancy has been analyzed on its own, showing the results of a malignancy-only group of patients undiluted by a group of patients with a uncertain or inconclusive histologic typing. Another limitation for recurrence and survival is the varying times of follow-up, ranging from 0 to 5 years and over, meaning the long term survival rate cannot be evaluated for the whole group. The follow-up of the kidney function seems to have the same issue, this has not been followed-up accurately due to the follow-up in different hospitals, explaining the missing numbers.

Three patients underwent an open nephrectomy, this was decided based on the expectation of a challenging surgery, caused by complex kidney problems and/or previous abdominal surgeries which resulted in plenty of scar tissue or a previous abdominal surgery was deemed too challenging already.

Despite the size of both groups and the results found, these patients are not randomized or blinded, resulting in a significant bias, this is the result of the character of this retrospective study. The doctors and patient made the decision for the optimal treatment at the time together, not within the context of a study. Comparisons between the two groups can be made whilst keeping the significant bias in mind, based on the literature these patient groups would be different.

Conclusion

Patients undergoing a (partial) nephrectomy were younger and in better overall condition than the patients that underwent a cryoablation. The (Partial)Nephrectomy group showed a higher rate of complications following the procedure. Percutaneous cryoablation has a higher recurrence rate as well. Overall survival seems rather similar, with cryoablation having a few more deaths, this might be caused by the less healthy patient selection. These results are relevant when counseling a patient in their decision for treatment. This being a retrospective study, conducting a randomized controlled trail would be preferable in regards to comparing both treatment methods.

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