SAHLGRENSKA ACADEMY

Long-Term Outcomes of Percutaneous Radiofrequency Ablation of Small Renal Tumours

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ABBREVIATIONS

SRM - Small Renal Masses

US - Ultrasound

CT - Computed Tomography

RCC - Renal Cell Carcinoma

RFA - Radiofrequency Ablation

WCRF - World Cancer Research Fund

VHL - Von Hippel-Lindau syndrome

MRI - Magnetic Resonance Imaging

BMI - Body Mass Index

AI - Artificial Intelligence

TKI - Tyrosine Kinase Inhibitors

IO – Immunotherapy

TNM – Tumour, Nodes and Metastasis

PCKD - Polycystic Kidney Disease

AML – Angiomyolipoma

MWA – Microwaves Ablation

OS - Overall Survival

CCS - Cancer-specific survival

PN - Partial Nephrectomy

SU – Sahlgrenska University hospital

ABSTRACT

Degree project, Programme in Medicine.

Title: Long-Term Outcomes of Percutaneous Radiofrequency Ablation of Small Renal Tumours.

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Background: Ablation technique is relatively new nephron-sparing treatment of small renal masses (SRM). It carries a lower complication rate and lower overall healthcare costs compared with surgery. However, there are only a few studies with long-term follow up. Therefore, further studies are needed to evaluate the long-term oncological outcome of percutaneous radiofrequency ablation therapy before this method can be applied on a general population of patients with SRM.

Methods: A retrospective evaluation was done on 101 patients with small renal tumours who were treated with percutaneous radiofrequency ablation (RFA) between 2002 and 2013 at Sahlgrenska University Hospital. The long-term outcomes of these procedures were studied and data was collected from patients' medical records.

Results: The Median follow-up time was 8.5 years. The total proportion of local recurrences was (17%). Five of them (29%) appeared during the sixth year of the follow-up. Also, the median time to local recurrence was 26 months. Three new metastases were detected under

the follow-up time and no late complications registered in this study. The median overall survival for the material was 9.0 years.

Conclusions: RFA has a good clinical value as a nephron-sparing method treating small renal tumours. Long-term results showed no late complications and relatively low metastasis and late recurrence rate. However, due to late occurring recurrences, longer follow-up than the standard of five years used after cancer surgery is required after RFA of SRM. Patient selection based on tumour characteristics, co-morbidity and estimated residual life is of paramount importance.

Keywords: Renal cell carcinoma, percutaneous radiofrequency ablation, Long-term outcome.

BACKGROUND

Epidemiology:

Renal cell carcinoma (RCC) accounts for approximately 90 % of all kidney malignancies. According to the World Cancer Research Fund (WCRF), RCC is the ninth most common cancer in men and the 14:th most common cancer among women in the world. In Sweden, it represents about 2.3 % and 1.5% of all cancer in men and women, respectively. The incidence of RCC in Sweden is about 1200 cases per year, and it is increasing, probably due to increased detection with the increased use of digital imaging, especially computed tomography (CT) [1].

Males have a 1.5 higher risk compared with females, and the patients are often over 60 years old when being diagnosed. It is less common in patients under 40 years old, but renal cancer can occur at any age [2].

98% of all renal cancers are unilateral when first diagnosed, however, patients with von Hippel-Lindau syndrome or another hereditary kidney disease are usually diagnosed with multiple and bilateral renal tumours [3].

About 60% of tumours are incidentally diagnosed by abdominal imaging performed for unrelated reasons, and 40 % are discovered with the presentation of symptoms such as haematuria. Studies have even shown that up to 76% renal cancer measuring less than four cm is discovered incidentally by computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound examination (US).

According to data in the National Swedish Kidney Cancer Register, about 15% of the patients have metastases already when first diagnosed. Also, 20% of patients treated for localised

disease develop tumour recurrence within five years. About 500 patients died from kidney cancer each year between 2010 and 2015 in Sweden. Overall, the 5-years survival is increasing, and it was 85% in patients with localised RCC and 15% in primary metastatic disease in 2015 [1].

Known risk factors for RCC are smoking, high body mass index (BMI) and arterial hypertension. It has been estimated that smoking is causing 20-35% of all RCC. Besides, hereditary genetic kidney disease increases the risk for renal tumours. Another factor is long-term dialysis that causes acquired kidney cystic disease and increased risk for renal tumours [1]. Most renal cancers are sporadic. However, 3-5 % is hereditary. These genetic tumours occur at lower age compared to sporadic ones and are often multiple and bilateral. The most common genetic syndrome that causes RCC is Von Hippel-Lindau disease (VHL). It is a genetic disorder caused by chromosome 3p deletion. This syndrome may include retinal angioma, hemangioblastoma and phaeochromocytoma which call for multidisciplinary care of these patients [3].

The incidence of renal tumours has increased in the last decade. In Sweden 2015, 64% of all patients were diagnosed incidentally by abdominal imaging while examining due to unrelated medical reasons. Consequently, tumour diameter has decreased due to earlier diagnoses of RCC and the 5-years survival has increased. Considering that a substantial proportion of renal tumours are overlooked in the clinical routine, incidental detection of RCC might increase further with more thorough routine scrutiny of the kidneys, irrespective of the primary indication of the examination, possibly with the help of artificial intelligence (AI) in the future [4].

Patients with renal tumours rarely have symptoms in the early stage of the disease, and

usually, the tumour has grown large or spread when symptoms occur. In symptomatic cases, 50% have haematuria, 40% flank pain, and 20% a palpable mass. Today, less than 10 % have this classic triad, i.e. the combination of these three symptoms.

The most common metastatic sites are lungs (50-60%), mediastinum, bones (30-40%), lymph nodes, adrenal glands, liver (30-40%), skin and brain (5%). Metastases can occur with all tumour sizes. However, there is a relationship between tumour size and frequency of distant metastases, therefore small tumours (less than three cm) are rarely metastatic.

Treatment of metastatic renal tumours is usually oncological. Today, tyrosine kinase inhibitors (TKI) or immunotherapy (IO) with checkpoint inhibitors is used. The treatments cause increased progression-free and overall survival, but the cancer is rarely cured. Cytoreductive nephrectomy is recommended for patients with good performance status and low metastatic burden compared to the size of the primary tumour. Metastasectomy is considered in cases with solitary metastasis or few metastases in one organ in the absence of negative prognostic factors [5, 6].

Classification of Renal cell carcinoma

Renal tumours are classified into 16 different entities according to the World Health Organisation and are defined based on their histopathological, genetic, and molecular features.

Malignant tumours:

The most common malignancy type is clear cell renal carcinoma (70-80%) which consists of cells with clear cytoplasm.

Papillary renal cell carcinoma (10-15%) usually consists of multiple papillary growths. Cells are usually small with pale cytoplasm. Basophils and eosinophils might be seen in the microscope. Papillary renal carcinoma is divided into two subgroups, type 1 (5%) and type 2 (10%). Recent studies have shown that patients with type 2 papillary carcinoma have a worse prognosis than patients with type 1 [7].

Chromophobe renal cell carcinoma (5%) is related to oncocytoma, which is considered a benign tumour. Usually, chromophobe tumours grow large and solid. Cells often have pale cytoplasm or eosinophil granular cytoplasm (microvesicles). Chromophobe renal tumours are often hypodiploid due to its genetic disorder (chromosome 1, 2, 6 deletion).

Collecting duct carcinoma is an aggressive, rare form of renal cancer that can appear in all ages but with a tendency to occur in younger patients. Those patients usually have no symptoms and therefore it is diagnosed at an advanced stage. However, symptoms such as haematuria and flank pain may appear in some patients.

Clear cell and papillary RCC have their origins in the proximal tubule cells in the kidney, while chromophobe RCC and collecting duct carcinoma have originated from the distal nephron.

However, 3-5% of all renal tumours are unclassifiable and cannot be categorized under the previously mentioned carcinomas. Other renal tumours in the kidney, such as Wilms tumours or renal pelvis cancers are not considered as renal cell carcinoma [8].

Metastases and general diseases such as lymphomas may also engage the kidneys. Renal cancers are staged according to the TNM system (T: Tumour: size and extension of the tumour; N: nodes: Tumour spread to regional lymph nodes; M: metastasis: spread to a distant

organ). The tumour's cells are classified according to Fuhrman Nuclear Grade and the International Society of Urological Pathology (ISUP) grading system [7, 9, 10].

Renal cysts:

Benign cysts are the most common expansive lesions in kidneys. Cysts are uncommon at younger ages, but more than 50% of all people above 50 years of age have one or several renal cysts.

CT, magnetic resonance imaging (MRI) or ultrasound can be used to diagnose renal cysts. A simple cyst appears with a very thin wall, clear content and no contrast enhancement after intravascular contrast medium administration. Usually, cysts cause no symptoms, and therefore neither treatment nor follow up are needed. Rarely, they may be very large and thereby symptomatic due to pressure on the urinary tract. Treatment in those cases is percutaneous puncture of the cyst and/or surgery with "deroofing" of the cyst wall.

Complex or atypical cysts are cysts that do not fulfil the criteria for simple cysts. Thus, they may exhibit thickened wall, septations, calcifications or solid parts, with or without contrast enhancement. Depending on the complexity and occurrence of contrast enhancement, complex cysts are classified according to the Bosniak system as Bosniak 1, 2, 2F, 3 or 4, where Bosniak 2F, 3 and 4 are associated with malignancy in 5-10%, 50% and 95-100%, respectively [11].

Polycystic Kidney Disease (PCKD) is a genetic disorder with a prevalence of about 0.5-1/1000. It is an autosomal dominant disease that can appear in childhood, but usually, it appears at 30-50 years of age. The patient develops multiple bilateral renal cysts, often combined with cysts in the liver, spleen and pancreas. Symptoms include hypertension, haematuria and flank pain. Due to the increasing number of large cysts, the kidneys become

markedly enlarged, and the patients often develop a gradual decrease of renal function, sometimes leading to uraemia [12].

Benign tumours:

Various histological types of benign tumours can grow in the kidney and which do not metastasise to other body organs:

Oncocytoma is a non-cancerous kidney tumour that usually presents as an incidental finding without symptoms. It is a solid tumour that may sometimes be large, and it can be bilateral. It develops from the distal convoluted tubule with some similarity to the chromophobe renal cell carcinoma. 30-50% of oncocytoma tumours show a central scar and well-defined edges surrounding a homogeneous dysplastic tissue. The name oncocytoma is derived from the fact that oncocytes cells, which are eosinophils, are seen under the microscope. Radiologically, it is difficult to distinguish it from a malignant renal carcinoma. Unfortunately, its' star-shaped scar may be seen centrally in both oncocytomas and renal cell carcinoma. Furthermore, it cannot be diagnosed until a biopsy is taken, alternatively at a histological analysis postoperatively.

Angiomyolipoma (AML) is a non-cancerous tumour with mixed content of fatty tissue, muscle tissue and blood vessels. The majority of cases occur as an isolated, incidental finding, without causing symptoms. 20% of all cases are associated with an autosomal dominant disease known as tuberous sclerosis. This rare genetic condition causes mainly benign tumours to develop in different parts of the body such as the brain, skin, kidneys, heart and lungs. The most dreaded complication of angiomyolipoma is retroperitoneal bleeding that may require arterial embolization or open surgery. Usually, only tumours larger than five cm cause symptoms. Angiomyolipomas have a typical appearance on CT due to its fat content

which usually makes it easy to diagnose. Fat-poor angiomyolipomas may, though, simulate renal cell carcinoma, and a renal cell carcinoma might occur simultaneously with AML [12].

Other types of non-cancerous renal tumours are rare and are often asymptomatic. Some examples are leiomyoma, fibroma, lipoma, lymphangioma and haemangioma.

Radiological hallmarks:

The primary method to diagnose renal cell carcinoma (RCC) is CT without and with the administration of intravenous contrast medium. In general, renal tumours show hyperattenuating in the nephrogenic and delayed phase of the CT. To determine if the suspected mass is viable or not, a difference of 15- 20 Hounsfield units should be noticeable at CT without and with contrast. In some cases, patients may present with kidney failure which can prohibit the use of CT-contrast medium injection. In such cases, an MRI can be performed instead [13].

It is important to do a full description of the tumour's size, organ involvement, distant metastasis, location of the tumour and the relation to the nearby structures before any surgical procedure. CT-angiography can be used as a mapping tool before resection. CT of the chest is recommended to determine if the patient has lung metastases. A percutaneous biopsy should be taken before any non-surgical procedure, such as ablation treatment, and is recommended before active surveillance [14].

Treatment of localised kidney tumours:

Surgery has always been the first-line therapy for patients with non-metastatic renal tumours in patients without significant co-morbidity. Radical nephrectomy means the removal of the whole kidney, renal fascia and possible lymph nodes. It is used in large or locally advanced

tumours, and in patients with vena caval tumour thrombus. Partial nephrectomy (nephron-sparing surgery) means excision of the tumour with a rim of surrounding healthy parenchyma, while the rest of the kidney is left in place. Partial nephrectomy is recommended for patients with (T1a, T1b) tumours and normal contralateral kidney (elective indication) and is always considered in patients with single or bilateral tumours or substantially decreased kidney function (imperative indication). Long-term follow-up has shown higher mortality and morbidity due to the high risk of chronic renal insufficiency when preforming radical nephrectomy on patients with small renal tumours. Partial nephrectomy can be done by three different methods, conventional (open surgery), laparoscopic or robot-assisted laparoscopy. The robot-assisted technique may be advantageous regarding morbidity, bleeding risk and ischemic time [15, 16].

Ablation therapy is a newer nephron-sparing technique. Thermal ablation can be performed using cryoablation, which uses extreme cold to freeze and kill the tumour cells. Alternatively, heat ablation, which uses high temperatures to burn the tumour locally with minimum damage to neighbouring healthy tissue. Heat ablation can be applied with radiofrequency waves or microwaves. Ablation methods are typically used for elderly patients with high surgical risk. Also, they are used for recurring renal tumours, and in patients with genetic kidney cancer such as von Hippel Lindau disease. Those patients may require multiple treatments. In most cases, renal tumour ablation therapy is done percutaneously, but it can be done laparoscopically or in open surgery, depending on tumour location. Treating renal tumours of less than three cm has shown the best results A tumour biopsy should be taken before treatment, either in a separate session or immediately before the actual ablation procedure.

Cryoablation (Cryo):

Cryoablation is a technique based on freezing the tumour to destruction. It is done by a cryoprobe that contains liquid nitrogen or argon. The probe inserted centrally in the tumour reduces the tissue temperature down to (145-190) ℃ below zero. This process creates an "ice ball" that causes coagulation necrosis of the tumour cells. To assure a good outcome, this procedure is repeated in the same spot. Cryoablation is a suitable method to treat renal tumours measuring up to 3 or 4 cm, with an endophytic or central location [17].

Some patients can be followed up as active surveillance when they are diagnosed with small renal tumours less than three cm, due to the correlation between low malignancy (Fuhrman grade 1-2) and small renal tumours. CT or sometimes ultrasound is used to monitor any progression in these patients [18, 19].

Radiofrequency Ablation (RFA):

RFA is one of the first heat ablation methods that destroy tumour's cells via an electrode and an RF-generator transferring high-energy radio waves. The electrode is inserted percutaneously with ultrasound or CT guidance. The RF-generator produces high tissue temperature (up to 100 ℃). Tumours smaller than three cm can be treated with a single electrode. Larger tumours can be treated by applying heat in different parts of the tumour, or by using a cluster electrode which has several antennas [20].

Treating renal tumours with heat ablation requires preoperative evaluation regarding location and size in different image planes. It has been shown that the smaller the tumour is, the better the results [21, 22].

Regarding tumour location, it is easier to treat posterior and lateral lesions percutaneously

compared to anterior and medial ones. These latter lesions may be better approached with laparoscopic surgery. In addition, tumours located centrally in the kidney are not as suitable for this type of treatment because of the “Heat-sink” phenomenon. “Heat-sink” phenomenon means that heat does not distribute uniformly through the tissue due to cooling by the high vascularity in the same region. [23].

Other contraindications include the presence of ureter or bowel within 1 cm of the treated zone, and obstruction of the puncture tract by intervening other organs such as spleen, liver or lung. Besides, treating tumours located near the abdominal muscles may cause greater pain postoperatively. If the bowel is at risk because of proximity to the tumour, fluid such as sterile water or glucose (hydrodissection) or carbon dioxide gas can be injected into the tissue between the tumour and the bowel [24].

It has been found that patients with multifocal tumours are good candidates for percutaneous RFA with better renal functional outcomes compared with surgery. Patients with solitary renal tumour treated with RFA have shown better preservation of renal function compared to patients who underwent partial nephrectomy [25].

It is of great importance to take a biopsy preoperatively or during the ablation to get a reliable diagnose. It aids with the planning of postoperative follow-up and future examinations. Preoperative conventional laboratory testing including serum electrolytes, coagulation parameters, serum creatinine and urine culture are required before ablation [14].

RFA is done under general or local anaesthesia. A Foley catheter is placed in the bladder to monitor for haematuria during the procedure. Radiofrequency ablation can be performed by

ultrasound- or combined CT/ultrasound -guidance to ensure that the probe is inserted correctly centrally in the tumour zone [23].

After inserting the probe connected to a temperature- or impedance-based generator the heat is increased gradually to a maximum of 100 ℃) and a maximum power of 200 Watts. Usually, tumours are treated during 10-15 minutes irrespective of size. To prevent bleeding and tumour cell seeding while withdrawing the probe, a tract ablation is performed at the end of the procedure [23].

Postoperative CT is done to confirm successful ablation. It is also needed to identify if any complications have occurred. American Guidelines recommends a follow-up CT or an MRI within three, six and twelve months' post-ablation. Thereafter, yearly radiological follow up is recommended for five to ten years based on patient's age and general condition. Enhancement of contrast medium in the ablation zone or enlarging of its size represents a strong sign of tumour recurrence [14].

Microwave ablation (MWA):

A newer method of thermal ablation destroying the renal tumour cells by heating the interior of the tumour is using microwaves as a mediator transforming the temperature. These microwaves constitute electromagnetic radiation with wavelengths ranging from 0.1 up to 100 cm and a frequency of 900 MHz or 2.4 GHz. MWA offers a more extensive ablation area in a shorter time and is not limited by the heat sink effect, desiccation or charring [26]. However, further data are needed to study the mid- and long-term follow up in order to determine its oncological effectiveness [27]. So far, ablation therapy is usually considered only if surgery is unsuitable, due to the lack of long-term oncological follow-up results [3, 17].

Ablation as standard treatment:

The use of thermal ablation as a treatment of small renal tumours is relatively a new phenomenon. There are only a few studies with long follow-up time. Gervais et al from MGA in Boston reported the oncological outcome of RFA of T1a tumours (n = 143) with a median follow-up time of 6.4 years [28]. They reported 4.2% local recurrence with a median time to diagnosis of 2.5 years. This study did not include patients with prior renal cancer treatment.

Another study done by Johnson BA et al from the University of Texas RFA treated 106 patients with an average tumour size of 2.5 cm [29]. The median follow-up time was 6.6 years and 10 recurrences were diagnosed. Kaplan-Meier 6-year "Cancer-specific survival" (CCS) was 96%.

Therefore, we think that the long-term oncological outcome of ablation need to be evaluated before it can be applied on a general population of patients in the future.
Our centre has previously published two articles presenting short-term outcomes of percutaneous radiofrequency ablation both ultrasound US-guided and combined US/CT-guided RFA [20, 30]. The idea behind this study is to continue the work of those two articles, completing the follow up of the same cohort after at least five years of the ablation.

AIM

The main purpose of the study was to evaluate the clinical value of percutaneous radiofrequency ablation of small renal masses by studying the long-term outcomes after at least five years. The outcomes include tumour recurrence, distant metastases, late complications and death.

METHODS

Patient characteristics

A total of 101 patients with small renal masses were retrospectively evaluated. These patients were treated with image-guided radiofrequency ablation (RFA) between 2003 and 2013 in the Department of Radiology at the Sahlgrenska University Hospital, Gothenburg, Sweden. There were 66 male and 35 female patients Fig. 1. The first 41 patients were treated with ultrasound-guided radiofrequency ablation and thereafter a total of 60 patients were treated with combined CT/US-guided radiofrequency ablation. The mean age of the patients at initial ablation treatment was 70.1 years, range between 34 and 86 years Table 1. The main comorbidity was a cardiovascular disease found in 60 patients, and previous renal or other malignancy was found in 56 patients [30].

Patient eligibility

Patients chosen to get the treatment had small renal masses, co-morbidities, and/or had high surgical risk. Additionally, patients with reduced renal function and those who had been diagnosed with genetic RCC, i.e. von Hippel Lindau syndrome were included. Other indications included patients who did not accept active surveillance and patients with limited metastatic disease and a life expectancy of at least one year. Other indications included previous partial nephrectomy, multiple renal tumours or tumour in a transplanted kidney. Contraindications were acute illness and uncorrected coagulopathy [20].

Tumour eligibility

The mean size of the treated tumours was 27 mm (ranged between 13 and 50 mm) Table 1. Six patients had tumours larger than four cm but still were included due to the absence of other

available treatment options. Tumours size and location were measured preoperatively by CT or MRI. The tumours were categorised according to its location in the kidney as exophytic, parenchymal, central and mixed. The decision to treat was made by urologists and interventional radiologists in consensus [20].

Radiofrequency ablation procedure

The treatments were performed under general anaesthesia (except for three patients) by an experienced radiologist. The first group (n=41) was treated with ultrasound (US) guided RFA, while the second group (n=60) was treated with combined US/CT-guided RFA. Local anaesthesia was given directly at the site of percutaneous electrode introduction. Two tumour biopsies were obtained before ablation. The temperature was measured in treated tissue directly after ablation and temperatures below 60° C were indicators for reablation [20]. The probe was repositioned while treating larger tumours to ensure proper ablation zone covering the maximum volume of the treated tumour. To reduce the risk of haemorrhage and tumour cell seeding during probe removal, the probe tract was cauterised to +60° C [30].

Outcomes

The primary success rate was defined as "the percentage of tumours that were successfully eradicated following the initial procedure or a defined course of treatment" [31].

Local recurrence "describe the appearance over a follow-up of foci of untreated disease in tumours that were previously considered to be completely ablated" [31].

New tumour describes the appearance of new malignancy after a completed ablation but away from the ablation zone in the same treated kidney.

Survival: The National Cancer Institute has defined survival as "the percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The survival rate is often stated as a five-year survival rate. Also called overall survival rate" [32].

Cancer-specific survival: According to the National Cancer Institute, the cancer-specific survival rate is "the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time" [32]. In this study, the time for both survivals begins at the date of the first ablation.

Follow-up

The follow up was done with CT or MRI depending on the renal function of each patient. The success of RFA was considered when seeing the ablation zone covering the tumour completely. Evidence of complete tumour ablation was the lack of contrast enhancement on post-injection scans, which represented the volume of the RFA-induced coagulation necrosis. [20] The first imaging was done the day after RFA in the first group and directly after RFA in the second group, followed by several imaging controls scheduled at 3, 6, 9 and 12 months. Thereafter annual follow-ups were performed up to at least five years. Complications of heat ablation were classified using the Clavien-Dindo classification [33]. In case of incomplete ablation or tumour recurrence, a repeat ablation session was considered.

Long-term outcomes of these procedures in the cohort were studied. These include local recurrence, development of metastases, as well as late complications and time of death. Long-term outcomes were evaluated by reviewing the patients' radiology reports and medical

records.

Statistics

The definition of a successful treatment included the absence of contrast enhancement within the tumour on contrast-enhanced CT or MRI [30]. Outcomes such as recurrence, complications, new tumours, metastasis and death were documented. Local recurrence-free survival was estimated with the Kaplan-Meier method and analysed with the log-rank test. Also, Cox Regression and T-test were used to analyse if a correlation existed between the variables. In addition, the CT/US-guided RFA group was compared with the group treated with US-guided RFA regarding those outcomes. Statistical analyses are performed by using the WinSTAT statistics package (R. Fitch Software, Bad Krozingen, Germany) and IBM Statistical Package for the Social Sciences (SPSS)® software. A p-value <0.05 was considered statistically significant.

ETHICS

This study was approved by the Central Ethical Review Board at the University of Gothenburg, Sweden. Ref 167-12.

RESULTS

A total of 101 patients were treated with heat ablation (41 patients, with 44 tumours treated with US-guided RFA and 60 patients, with 61 tumours treated with US/CT-guided RFA) (Fig. 1). The total primary success rate was 92% (97/105), with an 82% success rate in the US-guided group and 100% in the CT/US-guided group. Supplemental ablation was required in the US-guided group due to incomplete treatment resulting in 91% complete ablation after two treatments in the US group (Table 1).

Biopsy was performed on 93 (92%) patients. Malignancy was shown in 66 (71%) patients, 11 (12%) were benign and 16 (17%) were non-diagnostic (Table 1).

The median time of clinical follow-up was 102 months (8.5 years) ranged between 62 and 196 months. The median follow up time regarding imaging and local recurrence was 61 months (5.1 years) ranged between 3 and 168 months. Thus, four patients had greater than 10-years follow-up.

Local recurrence

The total proportion of local recurrence was 17/101 (17%). Nine of the recurrences (22%) were detected in the US-guided group (n = 41), and eight local recurrences (13%) in the US/CT-guided group (n = 60). Repeated ablation was done in nine out of the 17 patients (Fig. 5). Local recurrence appeared again in three patients, and one of them got a third ablation. In this case, the tumour was aggressive, with several metastases, and the patient got local recurrence shortly after.

There was no significant difference in the proportions of local recurrence between the two series ($\chi 2$ p = 0.26). The median time to recurrence was 26 months. Nine (53%) of the

recurrences occurred after 24 months whereof five cases occurred during the sixth year of the follow-up (Fig. 3). The mean follow-up time for local recurrence (time from the first ablation to the latest CT/MRI) was 5.1 years, range3-168 month. The mean follow-up time for US-guided ablations was 5.7 years, and 4.9 years for US/CT-guided ablation. Statistical analysis showed no significant correlation between the risk for local tumour recurrence and patient's age (P= 0.63) nor the size of the treated tumour (P=0.86).

New tumours

Six patients (five in the US-guided group, and one in the combined US/CT-guided group) got new tumours after the first ablation in the same treated kidney (located slightly away from the ablation zone). Another ablation was done for three out of these six patients. One of them was a patient with Von-Hippel Lindau (VHL) disease and got new tumour again after two years from the second ablation, therefore a third ablation was done. However, a recurrence was detected shortly after. Furthermore, radical nephrectomy was done in this case. Another patient got a local recurrence after the second ablation.

Metastasis

Three patients (3%) developed metastases during the follow-up (Fig. 2). New Metastases occurred only in patients who had known non-renal malignancy before they underwent ablation treatment. The first patient (US group) had bladder cancer and developed skeletal metastases during the follow-up time. Unfortunately, the origin of the metastases could not be identified due to unperformed biopsy. The second patient (US/CT group) had prostate cancer and developed lung metastases. Biopsy showed RCC. The third patient (US/CT group) had previously been treated for lung cancer. Renal Metastases were detected in the nearby lymph node and RCC was confirmed. None of these patients developed recurrences.

Additionally, 10 patients (10%) had a metastatic disease before the treatment, of which eight patients were previously nephrectomised. One patient had known skeletal metastasis from RCC, and one patient in the US-guided group had residual tumour despite three repeated ablations). Of those 10 cases, five cases (50%) had local tumour recurrence. Statistical analysis showed no significant correlation between the risk for metastasis and patient's age (P=0.75) nor the size of the RF-treated tumour (P=0.88).

A summary of the long-term outcomes of RFA is demonstrated in (Fig. 4).

Survival

The median survival rate for the entire material was 108 months (nine years) (Fig. 6). The 6-year survival rate was 74% and the 10-year survival rate was 43%. There was no significant difference in the overall survival (OS) between the two treated groups. The median of overall survival time for patients with prior kidney cancer was 74 months (6.2 years). It was significantly shorter than the OS for patients without prior renal cancer, 114 months (9.5 years), $p < 0.05$ (Fig. 7).

Cancer-specific survival (6-year survival) was 95% and 10-year survival was 88% (Fig. 8). Cancer-specific survival in patients with normal contralateral kidney (6-year survival) was 96% and 10-year survival was 93% (Fig. 9). The median follow-up time regarding metastasis and death was 8.5 years (13.8 years for US-guided ablations and 7.0 years for the combined US/CT-guided ablations).

In total, 47 (47%) patients (29 in the US-group and 18 in the US/CT-group) died during the follow-up period. The median time to death was 64 months (5.3 years) ranged between 4 and 163 months. Two patients, who developed metastases during follow-up time, died from metastatic RCC. The third patient was still alive when the data was assembled. Additionally,

three patients died from metastatic RCC. Four patients with metastases died from causes other than metastatic disease.

Late complications

No late complications (after 30 days from the ablation session) were detected in this study.

DISCUSSION

The main purpose of this retrospective study was to evaluate the clinical value of percutaneous thermal ablation of small renal carcinomas by studying the long-term outcomes (5-10 years). The main risks are local tumour recurrence, metastasis, late complications and death. It was found that 17% of the patients got local tumour recurrence, 22% in the US-guided group, and 13% in the US/CT-guided group. The median time to recurrence was 26 months. Nine (53%) of the local recurrences occurred after 24 months whereof five cases occurred during the sixth year of the follow-up. The mean follow-up time for local recurrence (time from the first ablation to the latest CT/MRI) was 5.1 years (3-168 months). This indicates that long-term follow up is needed for ablation treated patients. Thus, more than the current standard 5-years follow-up, particularly, in cases of younger patients.

Median survival for the entire material was 108 months (9 years). The expected remaining life expectancy for the general population in Sweden at the age of 70 years is 16 years in Sweden. This shows that the group of patients with renal tumours treated with ablation therapy is highly selected, with significant comorbidities contributing to a shorter life-span.

In this study, there were only two patients who underwent a third ablation, one of them had VHL disease and the other had an intractable metastatic renal carcinoma. In both cases the treatment was insufficient and a radical nephrectomy was done in the patient with VHL disease.

Only three patients developed metastases during the follow-up time and all of them had a confirmed non-renal malignancy before the ablation. Histopathological examination showed metastases of RCC in two of them. Ten patients (10%) had metastases before RFA. The

majority (8) underwent nephrectomy before RFA. That increased the probability of developing metastases. Of all cases with metastases, two were unrelated to renal cancer.

There are very few, if any, studies with as long follow-up time as our study. Gervais et al from MGA in Boston reported the oncological outcome of RFA of T1a tumours (n = 143) with a median follow-up time of 6.4 years [28]. They reported 4.2% local recurrence with a median time to diagnosis of 2.5 years. At the last control, 92.3% of patients were cancer-free. This study did not include patients with prior renal cancer treatment.

Johnson BA et al from the University of Texas RFA treated 106 patients with an average tumour size of 2.5 cm [29]. The median follow-up time was 6.6 years and 10 recurrences were diagnosed. Kaplan-Meier 6-year "Cancer-specific survival" (CCS) was 96%. In the subgroup with at least 10 years of follow-up, CSS was 94% and the OS was 49% (in our study 95% and 43% respectively).

In another study from the same centre, the outcome of RFA was compared with partial nephrectomy (PN) of T1a tumours [34]. Patients with metachronous tumours were excluded. The median follow-up time was 6.5 years and after five years both CCS and OS were 97.2% in the RFA-treated patients. "Recurrence-free survival" was 91.7%.

In a registry study comparing percutaneous ablation with PN of T1a tumours, Kaplan-Meier CCS was approximately 95% and OS about 75% after five years [35]. The median follow-up time for CCS was 3.5 years and 4.3 years for the OS.

Another registry study compared thermal ablation, surgery and Active Surveillance (AS) to T1aN0M0 tumours in patients older than 65 years [36]. 9-year Kaplan-Meier CCS was 96.3%

and OS 88.6%. Survival at AS was significantly worse in comparisons with the other strategies.

Wha et al reported results of RFA of 200 patients with an average tumour size of 2.9 cm and age of 68 years [37]. The median follow-up time was 4.0 years. Five (2.5%) local recurrences occurred, all of which occurred after more than four years of follow-up. Four patients (2%) developed remote metastases. CSS after five years was 97.9% and OS was 75.8%.

Excluding patients with previous kidney cancer, 10-year CCS in our study was 93%, fully comparable to studies with similar inclusion criteria [34, 36]. Four of the patients with metastasis died for reasons other than metastatic kidney cancer.

The average patient age at the time of initial ablation in our study was 70 years. It has been shown that patients with kidney cancer who are 70 years or older have a ”competing cause” mortality rate of 28.2% after 5 years [38]. Elderly people have an increased incidence of morbidity. Additionally, it has been shown that multiple morbidities, which many patients in this study had, further reduces life expectancy. [39] These previously mentioned factors contribute to the low 10-year survival rate (43%) in our study.

Biopsies showed malignancy in 71%, while 12% were benign. This may have contributed to the outcome rate of both recurrences and metastases. In addition, 17% of biopsies were non-diagnostic, which might disguise higher malignancy rate.

The study has several limitations. It was a single-centre study and the material was relatively small. On the other hand, the study had consecutive recruitment and long follow-up time (10 years), and there are few similar studies in the literature. Differences in outcome between different retrospective studies, such as this one, can largely be explained by selection bias.

Another limitation was the reliance on radiological reports for diagnosis of recurrence. For the final establishment of the recurrence rate with thermal ablation, re-evaluation of the radiological examinations is needed.

Further prospective studies are needed to evaluate both short-term and long-term outcomes of this treatment method and to compare thermal ablation with nephron-sparing surgery, including younger patients. It is also unclear which of the alternative ablation methods, such as RFA, MWA, Cryo, to prefer in different clinical scenarios. This will guide further implementation of this treatment in a more general population of renal tumour patients.

In conclusion, RFA has a good clinical value as a nephron-sparing method treating small renal tumours. Long-term results showed no late complications and relatively low metastasis and late recurrence rate. However, due to late occurring recurrences, longer follow-up than the standard of five years used after cancer surgery is required after RFA of SRM. Patient selection based on tumour characteristics, co-morbidity and estimated residual life is of paramount importance.

Populärvetenskaplig sammanfattning på svenska

Långtidsresultat av värmebehandling av njurtumörer

Den stigande förekomsten av njurcancer under de senaste två decennierna beror till stor del på ökad diagnostik av små njurtumörer på grund av ökad användning av bilddiagnostik såsom datortomografi, ultraljud och magnetkameraundersökning. Över 60% av njurcancer i Sverige upptäcktes som bifynd vid sådana undersökningar. Dessa tumörerna är i allmänhet mindre och har bättre framtidsutsikter. Numera är njursparande kirurgi, d.v.s. tumören bortopereras men njuren kvarlämnas, standardbehandling vid tumörer upp till fyra cm. Det är dock en relativ stor operation och många patienter med njurcancer är äldre och kan ha komplicerade sjukdomar. För denna patientgrupp har man utvecklat en ny metod där tumören avdödas genom upphettning (värmebehandling), som kan utföras genom en nål som införes via huden. Denna teknik har lägre komplikationsgrad och lägre kostnader för sjukvården jämfört med kirurgi. Risken för återfall på längre sikt är dock ofullständigt studerat, därför behövs ytterligare studier för att utvärdera de långsiktiga resultaten av den nya metoden innan den tillämpas på yngre och i övrigt friska patienter med njurtumörer i framtiden.

En utvärdering gjordes på 101 patienter med njurtumör som genomgick värmebehandling som styrdes av ultraljud enbart (serie 1) eller av en kombination av ultraljud och datortomografi (serie 2) mellan 2002 och 2013 i Sahlgrenska Universitetssjukhuset. Det långsiktiga resultatet av dessa behandlingsmetoder studerades genom data som hämtades från patientens journaler.

Resultaten visade att 93 patienter av 101 blev komplett behandlade redan efter första värmebehandling. Senare fick 19 av patienterna en extra behandling p.g.a. lokalt återfall eller utveckling av nya njurtumörer. Andelen lokala återfall var 17% (17/101). Hälften av dessa

återfall kom inom 26 månader, men en tredjedel (5 patienter) inträffade så sent som under sjätte årets uppföljning. Det var ingen signifikant skillnad i andelen lokala återfall mellan de två serierna. Den genomsnittliga överlevnaden för hela materialet var 9 år. Nya tumörer inträffade hos sex patienter. Tre av dem erbjudes en ny behandling, men endast en behandlades fullständigt.

Studien talar för att värmebehandling av små njurtumörer ej ger några sena komplikationer och risken för uppkomst av dottertumörer är liten. Lokala återfall är relativt vanliga jämfört med kirurgi och kan förekomma upp till 6 år efter behandlingen. I dessa fall kan dock patienten i allmänhet botas med en kompletterande värmebehandling. Ytterligare studier med långtidsuppföljning fordras innan värmebehandling kan bli standardbehandling hos yngre och friska patienter med njurtumörer.

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Figures and tables

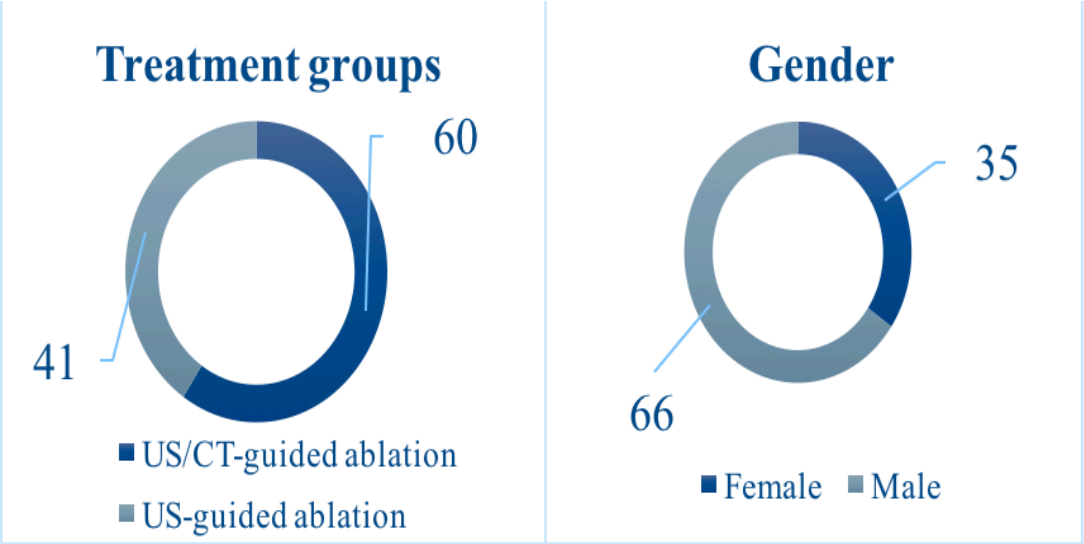

Fig. 1 Patient characteristics; treatment groups and gender in 101 studied patients. US: ultrasound. US/CT: Combined ultrasound/computed Tomography.

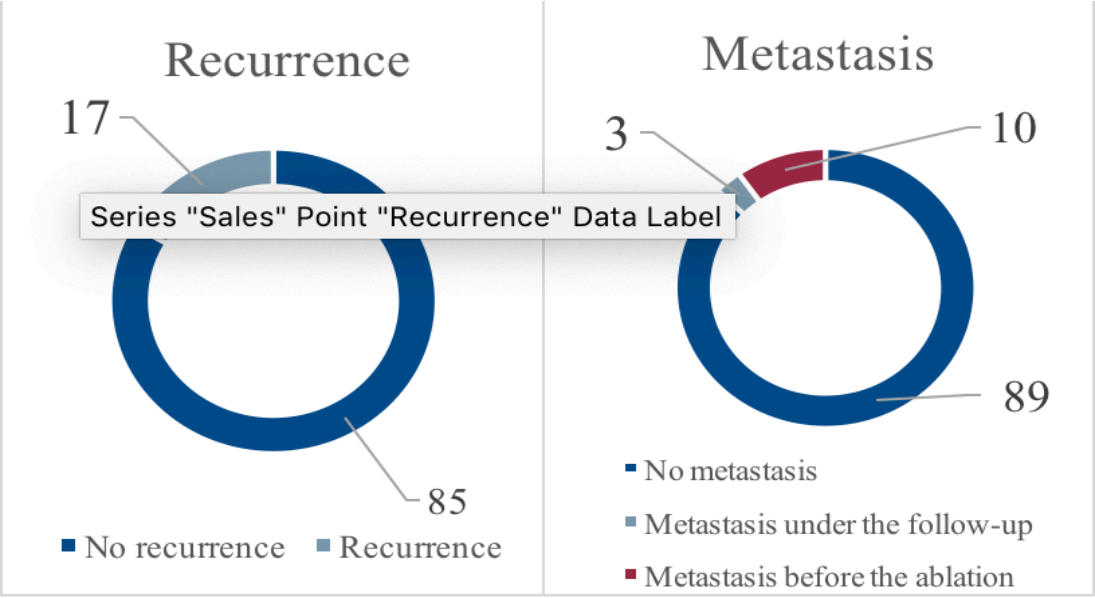

Fig. 2 The number of patients (of 101 studied patients) with/without recurrence and metastasis.

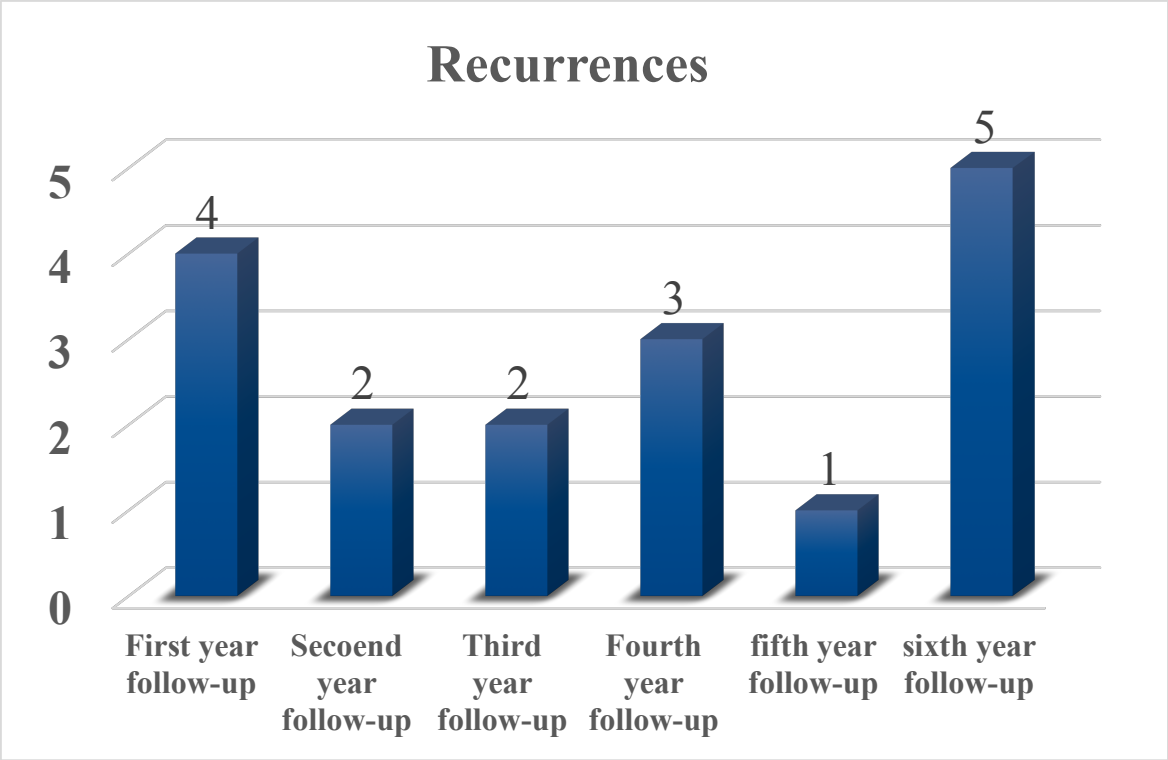

Fig. 3 Number of patients with recurrence recorded each year during the follow-up time.

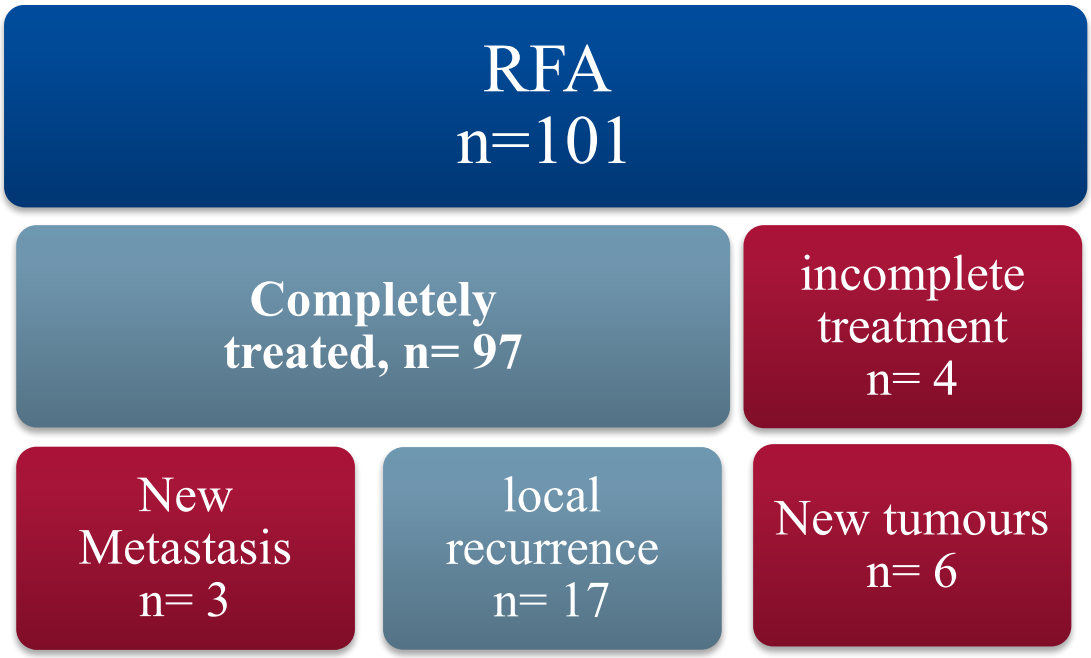

Fig. 4 Summary of the long-term outcomes after radiofrequency ablation (RFA) treatment.

Table 1 Patient, procedure and follow-up characteristics in 41 patients treated with ultrasound (US)-guided ablation and in 60 patients treated with combined ultrasound/computed Tomography-guided ablation.

CHARACTERISTICS	US-GUIDED RFA (41 PATIENTS)	COMBINED US/CT-GUIDED RFA (60 PATIENTS)	BOTH GROUPS (101 PATIENTS)
AGE, MEAN (RANGE)	70.1 (39–86)	70.1 (34–86)	**70.1(34–86)**
TUMOUR SIZE, MEAN SD (MM)	28.0 +/- 8.6	25.4 +/- 6.8	**27.01+/- 7.6**
PRIMARY TECHNICAL SUCCESS, N (%)	36/44 (82%)	61/61 (100%)	**92% (97/105)**
COMPLETED ABLATION AFTER 2 TREATMENTS, N (%)	40/44 (91%)	61/61 (100%)	**96% (101/105)**
MEAN FOLLOW-UP TIME FOR LOCAL RECURRENCE, YEARS (RANGE MONTHS)	5.7 (3-168)	4.9 (3-99)	**5.1 (3-168)**
LOCAL RECURRENCES, N (%)	9 (22%)	8 (13%)	**17 (17%)**
PATIENTS WITH NEW METASTASES DURING FOLLOW-UP (%)	1 (1%)	2 (3%)	**3 (3%)**
PATIENTS WITH PREVIOUS MALIGNANCY (%)	26 (63%)	31 (51%)	**57 (56%)**
MEAN FOLLOW-UP TIME FOR METASTASIS AND DEATH, YEARS	13.8	7.0	**8.5**

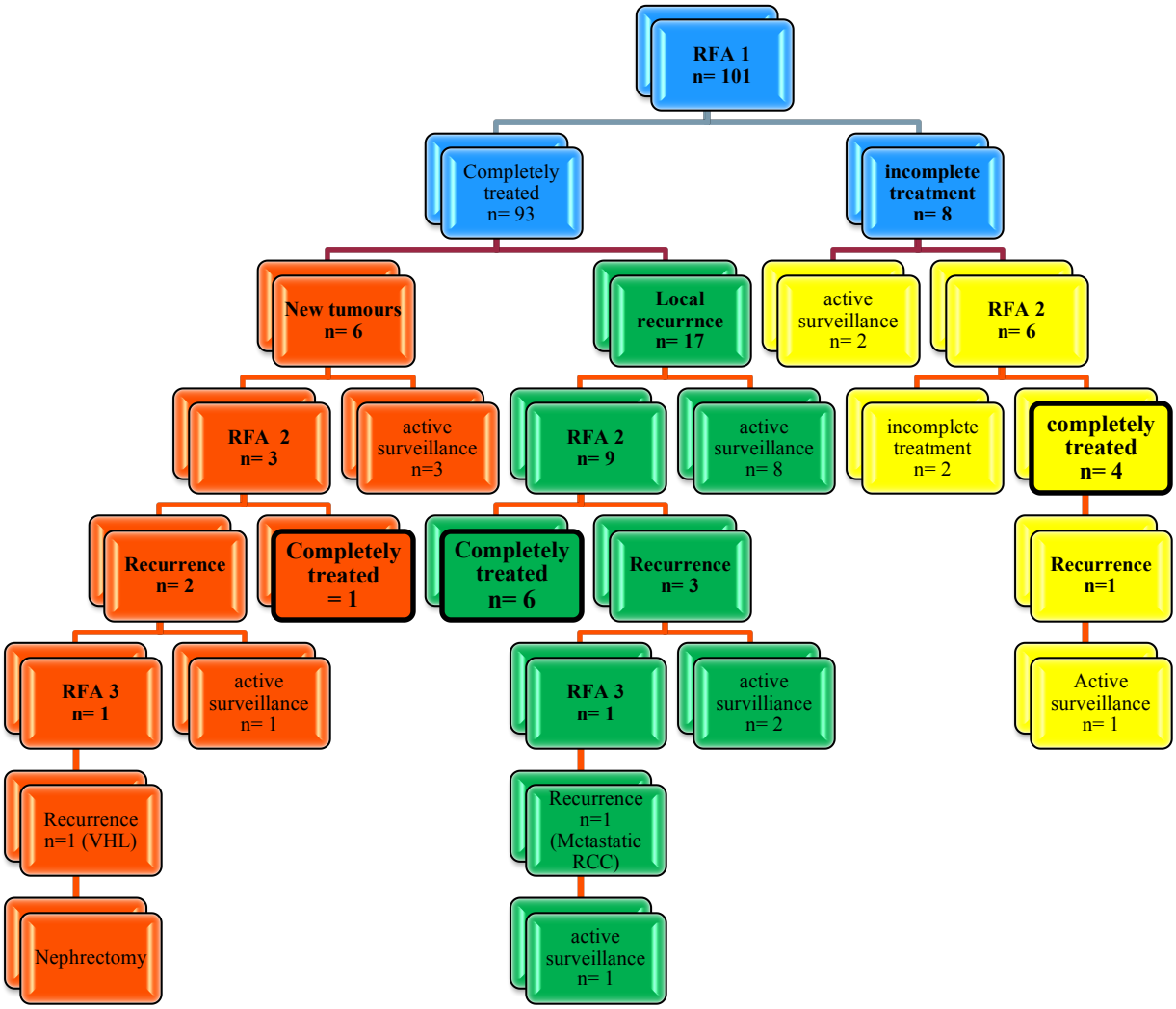

Fig. 5 Flow chart showing the results (complete/incomplete ablation, tumour recurrence and new tumours) of patients treated with radiofrequency ablation (RFA) from both ultrasound-guided ablation group and combined ultrasound/computed Tomography-guided group. (VHL: Von-Hippel Lindau syndrome. RCC: Renal cell carcinoma).

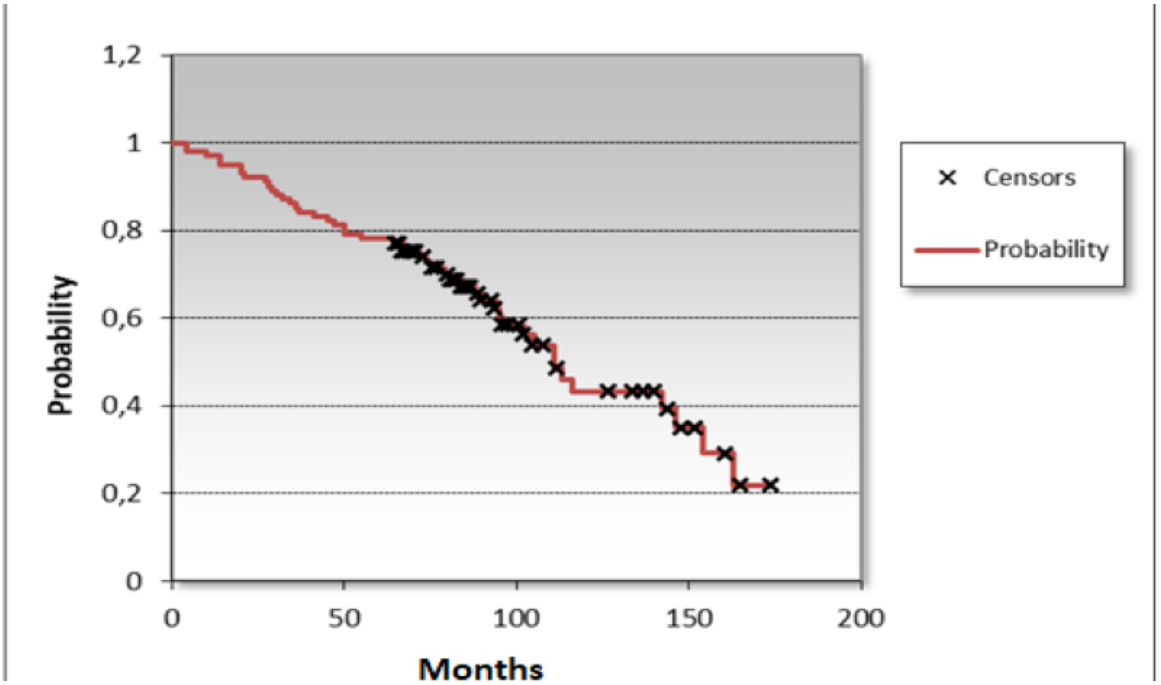

Fig. 6 Overall survival: The median survival for the entire material was 108 months (9.0 years). The 6-year survival rate was 74% and the 10-year survival rate was 43%.

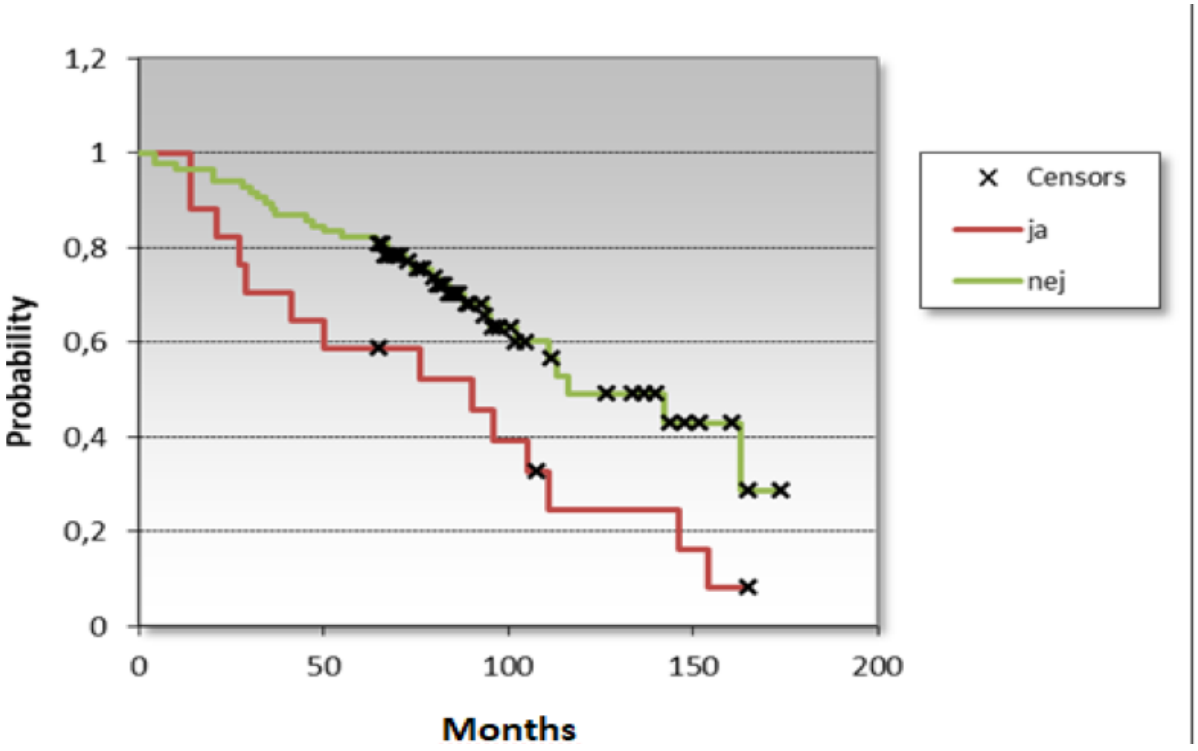

Fig. 7 Overall survival in patients with prior renal cancer was 74 months (6.2 years), significantly shorter than in patients without prior renal cancer (114 months = 9.5 years), p <0.05. (Ja: prior kidney cancer, Nej: without prior renal cancer).

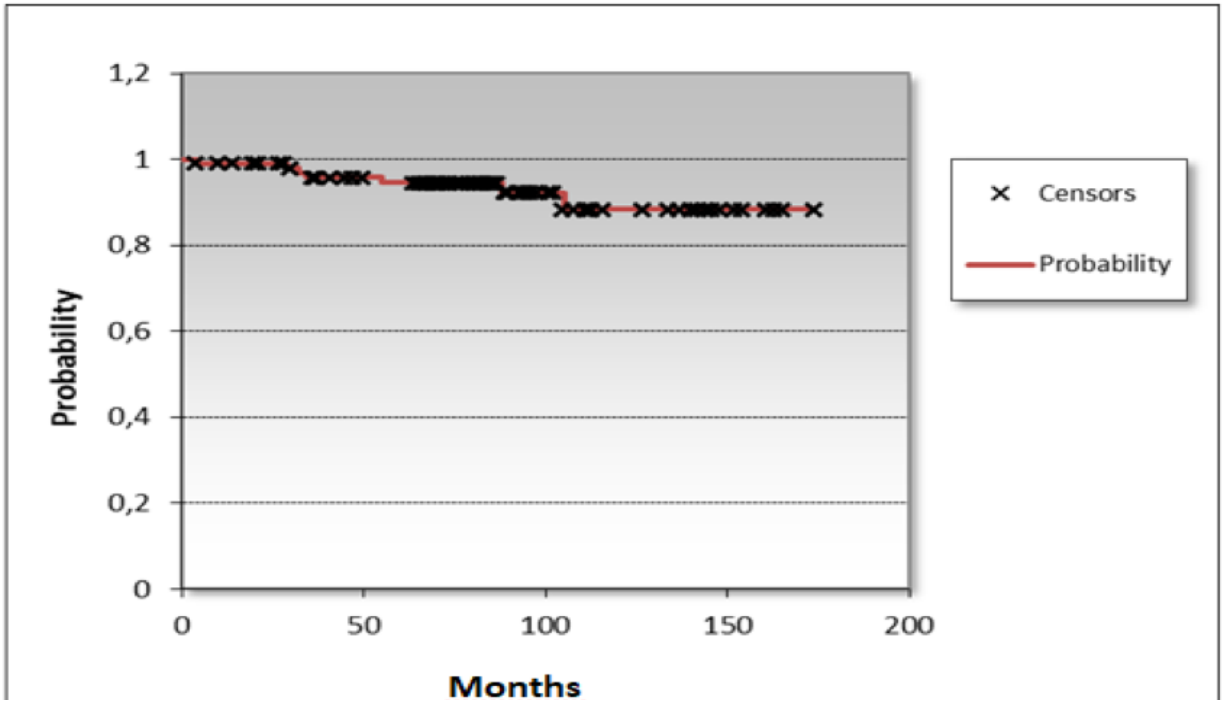

Fig. 8 Cancer-specific survival: (6-year survival) was 95% and 10-year survival was 88%.

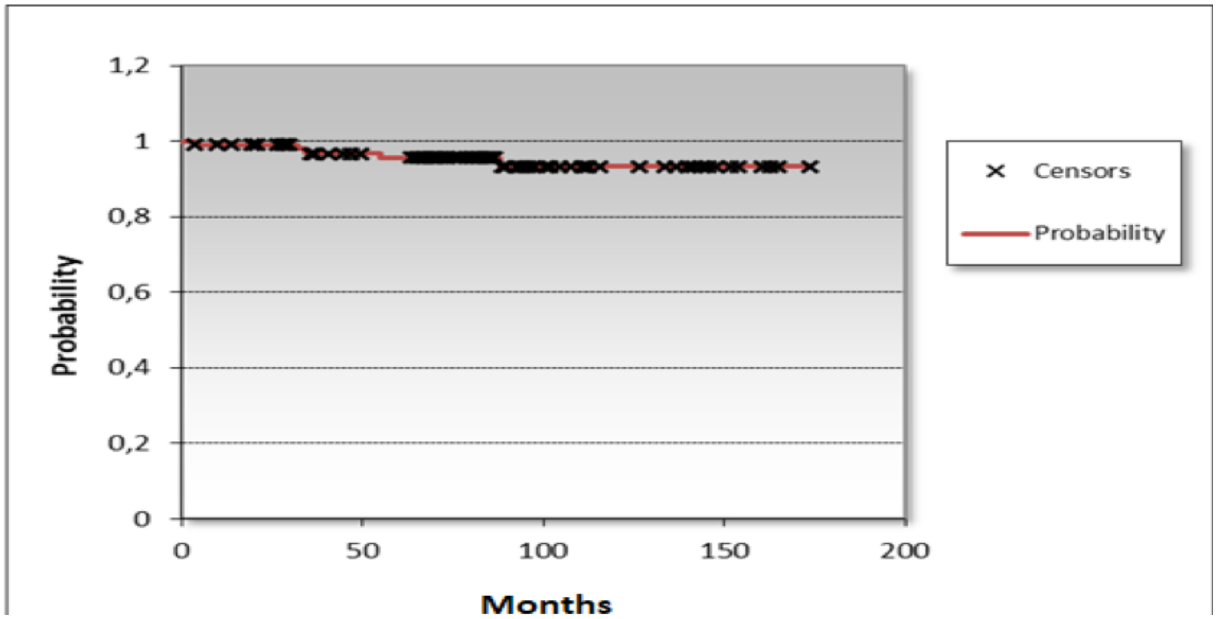

Fig. 9 Cancer-specific survival in patients with normal contralateral kidney (6-year survival) was 96% and 10-year survival was 93%.