Assessment of the effectiveness of radiofrequency ablation as a technique for destroying small renal tumors in patients older than 70

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Citation: Lesnyak O, Stroy O, Banyra O, et al. Assessment of the effectiveness of radiofrequency ablation as a technique for destroying small renal tumors in patients older than 70. Cent European J Urol. 2020; 73: 416-422.

Introduction During the past few decades, the percentage of older people in the population has been steadily growing due to the tendency of extended life expectancy. The efficacy of radiofrequency ablation (RFA) and tumor enucleoresection (TE) in the treatment of selected older patients with renal cell carcinoma (RCC) T1aN0M0 sized ≤4.0 cm has been a popular topic in many recent studies. The aim of this study was to access the effectiveness of radiofrequency ablation in patients older than 70 with T1aN0M0 RCC.

Material and methods A total of 86 patients aged 70–84 with histologically confirmed solitary kidney tumors T1aN0M0 who underwent RFA (n = 39) and TE (n = 47) were been included in this study. The patients were assigned to groups based on the impact of their comorbidities. Rockwood’s Clinical Frailty Scale Score (FS) and Charlson Comorbidity Index score (CCI) were used to separate fit from unfit older patients. The RFA group was characterized by an FS and CCI of 4–5 while the TE group had scores of ≤3. Five-year disease-specific survival (DSS), 5-yrs overall survival (OS) and relapse-free survival (RFS) were considered as criteria of treatment.

Results The 5-yr DSS in the RFA group was 97.4% vs. 95.7% in the TE group (p >0.05), while 5-yr OS was 74.4% vs. 80.9% (p <0.05) and RFS – 94.9% vs. 93.6% (p >0.05) respectively. Functioning of the operated kidneys did not deteriorate at the 6th and 12th month after RFA/TE as assessed by radioisotope renography. Conclusions In patients over 70 years of age, percutaneous RFA might be considered as an effective option for the successful treatment of T1aN0M0 RCC, as it preserves the functioning of the treated kidney and has oncological outcomes similar to TE.

Key Words: small renal tumors ‾ radiofrequency ablation ‾ tumor enucleoresection ‾ survival

INTRODUCTION

During the past few decades the percentage of elderly people in the population has been steadily growing due to the tendency of extended life expectancy. A proportion of the world has accepted the chronological age of 65 years as a definition of an ‘elderly’ or ‘older’ person, while that cut-off level in more
developed countries is higher. Whilst there are different approaches to stratify people aged 65 and older, some authors recently have proposed to classify them into three groups: youngest-old, ages 65 to 74 years; middle-old, 75 to 84 years; and oldest-old ≥85 years [1–4].

A significant portion of older patients is frail and has serious comorbidities, which limits the ability to perform radical surgery and/or general anesthesia. Conversely, due to adequate medical care and social stability, there exists a population of fit people over the age of 70 that are able to undergo surgery. To separate the fit elderly persons from the frail within the same age group, the commonly used Fried’s and Rockwood’s frailty scores have been proposed [5, 6].

Older patients require special protocols for adequate care depending on their surgical/urological pathology and general health status [7, 8]. Kidney cancer is a common urological pathology in seniors, therefore strict algorithms for their care must be created. Tumor enucleoreshion (TE) and radiofrequency ablation (RFA) are used for the treatment of selected patients with renal cell carcinomas (RCC) T1aN0M0 sized ≤4.0 cm. The oncological outcomes of TE and RFA in patients with such tumors have been a popular topic in many recent studies [9–12].

Expediency of surgery in older patients with RCC and benefits of active surveillance (AS) are constantly under discussion. Because of age and associated cardiovascular risks, even fit older patients with small renal carcinomas often are not suitable for long-term invasive surgical options under general anesthesia, like partial nephrectomy or simple nephrectomy. Thus, minimally invasive procedures, specifically those performed under local anesthesia, are preferred [13, 14].

The aim of this study was to access the effectiveness of radiofrequency ablation in patients with T1aN0M0 RCC aged older than 70 years.

**MATERIAL AND METHODS**

This study is a prospective observational cohort study, involving 86 consecutive patients with histologically confirmed solitary kidney tumors T1aN0M0 that had been treated in our clinics from 2008 to 2015 by RFA or TE and followed-up for 5 yrs. The Fuhrman grading system was used for histological verification [15]. Patients presenting with benign kidney tumors, history of synchronous multiple and bilateral tumors or hereditary RCC syndromes and/or younger than 70 or older than 85 years of age were not included in our study. To minimize the risk of intraoperative penetration of the renal cavity, we performed TE or RFA only in cases in which tumors were characterized by a distance of more than 10 mm from their edge to the renal collecting system. The patients were assigned to groups based on the impact of their comorbidities. In order to correctly separate fit from unfit older patients for our study, we used a modified Rockwood’s Clinical Frailty Scale Score (FS) and Charlson Comorbidity Index score (CCI). We chose the FS during recruiting because its exclusive graduated scale seems to be a more sensitive predictor for adverse health outcomes in comparison with Fried’s index concerning unexpected clinical outcomes [8, 16]. All enrolled patients in the TE group were characterized by Rockwood’s FS ≤3 compared to the RFA group who had scores of 4–5. CCI in patients who were selected for TE was below 4, while for the RFA group we selected patients with a CCI of 4–5 [17].

TE was performed only in cases with the presence of a tumor capsule, with an extrapleural retroperitoneal lumbar approach. The kidney was revised, then mobilized and peritumoral fat was left in situ. The kidney pedicle was carefully isolated and the renal artery was clamped manually or instrumentally before the first incision was made on the renal capsule surrounding the tumor. The incision of the kidney capsule was performed up to 3 mm away from the visible edge of the neoplasm, after which the tumor was removed using scissors and a brain dissector. The tumor bed was inspected for signs of residual tumor tissue or bleeding. Intraoperative frozen application of the tumor bed was made, and visibly bleeding vessels were sutured. Finally, the tumor bed was carefully coagulated by means of diathermy for haemostasis, as well as for oncological reasons. The incision of the kidney parenchyma was closed using interrupted sutures. In cases of large capsular defects, available peritoneal tissue was used as a filler as per the recommendations [18].

In our series we performed RFA using Electrotom HITT-106 (‘Berchtold’, Germany) percutaneously under ultrasonography (US) control. We agree with Venkatesan AM et al, 2011, that compared to computerized tomography guiding, the advantages of using US for monitoring during renal ablation are a lack of ionizing radiation for the patient and doctors with convenient real-time capability [19]. Local anaesthesia was given along the tract up to the surface of the kidney. The RFA electrode was moved along the anesthetized percutaneous tract in such a way that its tip lied roughly 1 cm proximally to the geometric centre of the tumor. Under US guidance, we preferred to initially ablate the deeper parts of the tumor before the superficial portions were
RESULTS

A total of 86 patients (pts) in two groups met the selection criteria. The RFA group included 39 (45.3%) pts and TE group 47 (54.7%) pts. Two patients from the RFA group and two patients from the TE group presented with only one functioning kidney. All cohorts consisted of similarly aged older patients over 70 years of age. Male-to-female ratio was 1.2:1 (21/18) in the RFA cohort and 1.1:1 (25/22) in the TE group. Means of CCI, Rockwood’s Indexes and size of tumors are presented in Table 1. Patients from the RFA group were 76.4 ±5.7 years old while patients from the TE group were 77.8 ±6.1 years old (p >0.05). Means of body mass index (BMI) were 23.8 ±6.4 vs. 22.7 ±5.1 respectively (p >0.05). Mean tumor size at its
destroyed to prevent the obscuration of the deeper parts by microbubbles produced during RFA of the exterior portions. In patients with larger neoplasms, multiple overlapping ablations were performed to provide a complete thermal injury area of sufficient size to destroy the entire cancer and to guarantee the necessary tumor-free margin [20].

In cases of larger tumors [n = 4 (10.3%) pts] combined with inconvenient localization, we did not achieve complete percutaneous tumor ablation as registered by US. Therefore, we performed an intraoperative conversion into open RFA through a small lumbar incision that allowed us to freely manoeuvre the electrode without additional percutaneous tracts. Conversion into open RFA was made under general anaesthesia.

Obtained 5 year oncological outcomes of RFA in patients with RCC T1aN0M0 were compared with survival rates after TE.

For renal function monitoring we calculated glomerular filtration rate (GFR) and performed radioisotope renography (RRG) with 131-Iodine labelled sodium ortho-iодоhippurate (Hippuran). While GFR describes the functioning of both kidneys, RRG could be considered as an adequate method for unilateral renal function evaluation. GFR was calculated and RRG was performed before, as well as 6 and 12 months after RFA or TE. The following parameters were measured from renogram curves: 1. The time interval from injection to the peak of the tracing (TMAX); 2. The time interval from injection to the point where the curve decays to 50% of the maximum (T1/2) [21].

Patients were followed radiologically with the following imaging protocol: initial contrast enhanced CT was performed at the 3rd and 6th months, then every 6 months for 2 years and yearly for 5 years [22]. The Kaplan-Meier curves were created to determine 5-year disease-specific survival (DSS) and 5-year overall survival (OS) for TE vs RFA [23]. We also calculated and compared relapse-free survival (RFS) as the length of time after primary treatment for a cancer that the patient survives without any signs or symptoms of reoccurrence of the cancer. RFS was measured in both groups from date of surgery until recurrence and concluded at death or last follow-up. Survival curves were compared using the log-rank test. Differences in the distribution of parameters were presented by: Mean ± Standard Deviation (M ±SD). Statistical tests were two-tailed and p <0.05 was considered significant. Accordingly, medians and cut-offs of analysed parameters were calculated and verified using algorithms [24].

All patients provided signed informed consent for the study.

Table 1. Enrolled patients’ characteristics and their oncological outcomes

| Variables | RFA | TE | p     |
|----------|-----|----|-------|
| n, pts   | 39 (45.3%) | 47 (54.7%) | <0.05 |
| Age, years | 76.4 ±5.7 | 77.8 ±6.1 | >0.05 |
| Youngest-old (70–74 years), n (%) | 18 (46.2%) | 24 (51.1%) | >0.05 |
| Middle-old (75–84 years), n (%) | 21 (53.8%) | 23 (48.9%) | >0.05 |
| Male-to-female ratio | 1.2:1 | 1.1:1 | >0.05 |
| BMI | 23.8 ±6.4 | 22.7 ±5.1 | >0.05 |
| D, cm | 3.2 ±0.8 | 3.1 ±0.9 | >0.05 |
| D ≤3.0 cm, n | 24 (61.5%) | 28 (59.6%) | >0.05 |
| D >3.0 cm, n | 15 (38.5%) | 19 (40.4%) | >0.05 |
| CCI | 4.6 ±0.4 | 2.7 ±0.3 | <0.05 |
| FS | 4.7 ±0.3 | 2.4 ±0.6 | <0.05 |
| Fuhrman grade: | | | |
| G1 | 14 (35.9%) | 15 (31.9%) | >0.05 |
| G2 | 17 (43.6%) | 21 (44.7%) | >0.05 |
| G3 | 6 (15.4%) | 8 (17.0%) | >0.05 |
| G4 | 2 (5.1%) | 3 (6.4%) | >0.05 |
| Duration of procedure, min | | | |
| D ≤3.0 cm | 27.2 ±4.1 | 74.6±8.6 | <0.05 |
| D >3.0 cm | 45.4 ±7.5 | 96.3±10.4 | <0.05 |
| Complications, n (%) | | | |
| TOTAL | 4 (10.3%) | 6 (12.8%) | >0.05 |
| Clavien grade I | 3 (7.7%) | 3 (6.4%) | >0.05 |
| Clavien grade II | 2 (4.3%) | >0.05 |
| Clavien grade III | 1 (2.6%) | 1 (2.1%) | >0.05 |
| RFS, % | 94.9 | 93.6 | >0.05 |
| 5-year DSS, % | 97.4 | 95.7 | >0.05 |
| 5-year OS, % | 74.4 | 80.9 | <0.05 |
| Number of retreatments | 2 (5.1%) | 3 (6.4%) | >0.05 |

BMI – body mass index; CCI – Charlson Comorbidity Index; D – tumor diameter at its greatest dimension; DSS – disease-specific survival; FS – Rockwood’s Clinical Frailty Scale Score; n – number of patients; OS – overall survival; RFS – relapse-free survival
greatest dimension was 3.2 ±0.8 cm (95% CI) vs. 3.1 ±0.9 cm (95% CI) respectively (p >0.05). In patients who were selected for RFA, CCI was 4.6 ±0.4. This index in the TE group was 2.7 ±0.3 (p <0.05). Rockwood’s FS was 4.7 ±0.3 vs. 2.4 ±0.6 respectively (p <0.05).

RFA sessions lasted significantly shorter than TE. Means of RFA and TE duration in cases with tumors ≤3.0 cm at their greatest dimension were 27.2 ±4.1 vs. 74.6 ±8.6 min (p <0.05) while in larger tumors those values were 45.4 ±7.5 vs. 96.3 ±10.4 min respectively (p <0.05).

In our study of 39 RFA sessions, only 4 (10.3%) complications were registered. One of them (2.6%) was macrohematuria on the 3rd day after RFA. CT imaging was unremarkable, and haematuria stopped without treatment (Clavien grade I). Another patient (2.6%) developed an urinoma due to perforation of the renal collecting system at the ureteropelvic junction during ablation of a lower pole neoplasm. It was managed conservatively with ureteral stenting and resolved on its own; a follow-up intravenous urogram showed normal passage of urine (Clavien grade IIIa). In 2 (5.1%) patients with diabetes mellitus, we registered infections of the percutaneous tract that were effectively treated with antibiotics (Clavien grade I).

In the TE group we registered complications in 6 (12.8%) cases. Haematuria that stopped without treatment (Clavien grade I) occurred in 3 (6.4%) patients, fever managed by antipyretics and transfusions (Clavien grade II) in 2 (4.3%) cases, and urinoma caused by destruction of the renal collecting system that was managed by ureteral stenting in 1 (2.1%) case (Clavien grade IIIa).

During the 5 year follow-up, cancer-related lethal outcomes were registered in 1 (2.6%) patient from the RFA group (Fuhrman grade IV) and in 2 (4.3%) patients from the TE group (both Fuhrman grade IV) because of tumor progression and metastatic disease.

The 5-year DSS in the RFA group was 97.4% vs. 95.7% in the TE group (p >0.05). The 5-year OS in the analysed RFA and TE cohorts was 74.4% vs. 80.9% (p <0.05) correspondingly (Figures 1–2).

Tumor recurrence was registered in 2 (5.1%) patients from the RFA group and 3 (6.4%) patients from the TE group with a median time to recurrence of 11.6 (8.4–14.7) months and 10.4 (7.8–15.3) months respectively. Criterion for defining recurrence was a new enhancement at the place of the previous tumor localization as verified by CT. RFS in the RFA group was 94.9% vs. 93.6% in the TE group (p >0.05). In the RFA group we performed 2 (5.1%) retreatments by RFA because both patients were
considered unfit for nephron-sparing surgery. In the TE group, recurrences were managed in 2 (4.3%) cases by partial nephrectomy and simple nephrectomy in 1 (2.1%) case due to the technical impossibility of performing a partial nephrectomy. For the evaluation of renal function, we calculated GFR and performed RRG before and after treatment. Table 2 presents means of GFR, TMAX and T1/2 that were calculated during RRG of operated kidneys with small renal carcinomas. Four patients from the RFA group and six patients from TE group did not appear for follow-up visits at the 6th and 12th months after treatment, so they were excluded from that part of our study. As presented in Table 2, functioning of the operated kidneys did not deteriorate at the 6th and 12th months after RFA/TE treatment. Obtained results indicate the absence of negative effects of the studied techniques on renal function, which is extremely important in elderly patients, especially those with only one functioning kidney.

DISCUSSION

Renal cell carcinoma is a common urological pathology that is responsible of 5% of cancers in men and 3% in women. In the younger population, more men suffer from RCC while the male-to-female ratio is almost equal in patients older than 70 years [25, 26]. In this study we aimed to assess the role of RFA in the treatment of RCC T1aN0M0 patients older than 70 years of age. The obtained oncological outcomes were compared with results of tumor enucleoresection. The role of minimally invasive nephron-sparing surgeries in the treatment of patients with localized small renal carcinomas is a topic of numerous investigations [9; 13]. Puppo P. et al. assumed that not only partial or radical nephrectomies achieve high survival rates in patients. According to the authors, enucleoresection of small renal tumors surrounded by a minimal layer of grossly normal renal parenchyma reproduces the results of partial and radical nephrectomy with minimal morbidity as well as a 5 year survival rate of 95.7% (90/94 patients), a 5 year cancer-specific survival rate of 98.9% (93/94) and a disease-free survival rate of 98.9% (93/94) [27]. Adamakis et al. concluded that enucleoresection reproduces the same results as partial and radical nephrectomy in patients with small kidney carcinomas with an overall cancer-specific survival of 95.4%, an overall progression-free survival of 93% and minimal morbidity. The authors believe that TE is a safe and acceptable approach for elective nephron-sparing surgery [10].

Our results support those findings with comparable high survival rates after TE even in patients over 70 years of age. Although some contemporary researchers recommend RFA for renal tumors no more than 3 cm in their greatest dimension and consider larger ones to have poorer outcomes, we have demonstrated successful coagulation of 15 RCCs T1aN0M0 sized from 3 to 4 cm (Table 1) [28]. Such an approach is also supported by other authors. According to Wah TM et al., 2014, they successfully coagulated tumors of even up to 5.6 cm. However, the authors concluded that neoplasms bigger than 3.0 cm often require more than one percutaneous tract for RFA electrode that objectively extends the duration of the procedure and could also be harmful for the patient due to trauma by more than one percutaneous penetration in the same lumbar area [29]. The advantage of the percutaneous RFA approach that we used is that such access can decrease the risks of surgery for older patients.

The open access we used during the conversion of percutaneous into open RFA gave us the ability to destroy larger kidney tumors due to the increased manoeuvrability of the electrode until complete coagulation. However, the necessity of additional anaesthesia as well as a lumbar incision during open RFA could be considered as an important disadvantage of such an option in frail patients. Psutka SP et al, 2013, also reported high disease-free rates of up to 92.3% in patients with RCC T1a after RFA at 3.8-year median follow-up with a median tumor size of 3 cm (IQR: 2.1–3.9 cm) [30]. The significant advantage of RFA in RCC patients is its minimal influence on renal function that is extremely important in the elderly [31]. Our study also confirms the absence of renal function impairment after treatment with RFA or TE.

Apart from RFA or TE, active surveillance (AS) is one of the recommended management strategies for small kidney tumors. Data of the prospective Delayed Intervention and Surveillance for Small Renal Masses registry suggest that AS is not inferior to immediate intervention [32]. Furthermore, a meta-analysis performed by Pierorazio PM, et al., 2016, demonstrated high metastasis-free and cancer-specific AS survival rates, comparable to outcomes after thermal ablation or surgery [33]. The authors declared that patients of advanced age with numerous comorbidities, or those in which other conditions take priority at a given time can be selected for AS. However, in our opinion, the urgent question remains: “What to do with the youngest-old and middle-old patients with few comorbidities and confirmed RCC T1aN0M0?” Our data shows that
such patients who underwent RFA reported high 5-year DSS and RFS rates statistically equal to TE. The insignificant decrease of 5 year OS in the RFA group compared to TE [74.4% vs. 80.9% (p < 0.05)] seems to be a consequence of worse comorbid status in the RFA enrolled patients confirmed by higher Rockwood’s FS and CCI. The practical value of RFA is local anaesthesia that could be considered preferable in patients with comorbidities who cannot undergo nephron-sparing surgery. A significantly shorter duration of RFA comparing with TE can also be considered as an advantage of ablation (Table 1). Therefore, we believe that patients with T1aN0M0 aged 70–84 years with a high life expectancy should be managed by the same protocols as younger patients with the preferred selection of minimally invasive surgical options including percutaneous RFA. Charlson Comorbidity Index and Rockwood’s scale might be helpful tools for the selection of such patients. In our study all participants aged 70 to 84 were selected based on a CCI cut-off of 5 or below and Rockwood’s Frailty Score ≤5, with the possibility of promising results of treatment by RFA compared to their fit coevals with lower Indexes who were able to undergo nephron-sparing surgery. It has been proven that in patients ≥85 years of age with shorter life expectancy, results would be fundamentally different [34]. The possible tools and cut-offs for the selection of older patients with small renal carcinomas appropriate for RFA or TE could be a subject of future investigations.

Thus, it seems that the choice of surgical management for patients over 70 years of age with small renal carcinomas should be made based on an individual approach in each case and after the creation of special algorithms taking into account not only tumor characteristics and patient’s age, but also his/her health status at the time of tumor discovery.

CONCLUSIONS

In correctly selected patients over 70 years of age, percutaneous RFA might be considered as an effective option for the successful treatment of T1aN0M0 RCC that achieves high 5-year DSS, RFS and OS rates comparable to tumor enucleoresection. However, the application of the analysed techniques is limited by an intrarenal tumor localization and patients’ comorbidities, thus requiring the creation of special algorithms. CCI and Rockwood’s Frailty Scores might be valuable tools during the choice of treatment modality.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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