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Association among the R.E.N.A.L. Nephrometry Score and Clinical Outcomes in Patients with Small Renal Masses Treated with Percutaneous Contrast Enhanced Ultrasound Radiofrequency Ablation

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Number ID:	1833/2019/02
Type:	Original Basic Research And Clinical Articles
Domain:	Urological oncology
Corresponding author:	Cristian Konstantinidis; email: cristiank1979@yahoo.com
Conflicts of interest:	The authors declare no conflicts of interest.
Key Words:	renal cell carcinoma, small renal masses, radiofrequency ablation, R.E.N.A.L. nephrometry score, Contrast Enhanced Ultrasound

Introduction An association among the R.E.N.A.L. nephrometry score (RNS) and clinical outcomes in patients with a small renal mass (SRM) has been proposed. We analyzed clinical outcomes according the RNS in patients with a SRM treated with Percutaneous Contrast Enhanced Ultrasound (CEUS) Radiofrequency Ablation (RFA).

Materials and methods Patients with a SRM treated with RFA were retrospectively identified between January 2005 and March 2015. The association among RNS and clinical outcomes were evaluated using parametric and non parametric analysis.

Results We analyzed 163 SRMs in consecutive 149 patients. The mean age was 71.7 years. Mean follow-up time was 33.3 months +/- 20.6 (2-102). The mean RNS was 5.6 +/- 1.52 (4-11). Thus, 121 (74,2%) cases were of low complexity and 42 (25.8%) were medium complexity. We identified 11 cases of tumor persistence (6.7%).The mean RNS was 5.58 in the cases with no persistence and 5.73 in the cases with persistence (p = 0.788). We identified 15 (9.2%) cases of recurrence. The mean RNS was 5.57 +/- 0.1 (4-11) in the cases without recurrence and 5.73 +/- 0.4 (4-9) in recurrence cases (p = 0.804). Of the 76 biopsy proven RCC cases, 8 (10.5%) cases of recurrence were observed, 5 in the low complexity group and 3 in the medium complexity group (p= 0.690). 9 (5.5%) cases of complications were observed, with 5 (4.3%) in the low complexity group and 4 cases in the medium complexity group (p = 0.23). The mean length of stay was 1.5 days with a significant difference between low and medium complexity groups (1.3 vs 2.1 days, p= 0.02). The mean difference between preoperative eGFR and estimated at 12 months was

-3.08 mL / min +/- 13.3 (-49.4-34.1) and was significant (p = 0.008) however this variation did not show significant differences between the low and medium complexity groups (p = 0.936). All cause mortality was 11.7%, 14 cases (11.6%) in the low complexity group and 5 (11.9%) in the medium complexity group were identified (p= 1.0). No cases of RCC-specific mortality were identified.

Conclusions The RNS was not associated with tumoral persistence, recurrence, cancer specific mortality, complications or renal function 12 months after the first treatment showing significant difference only in length of hospital stay between low and medium complexity groups.

INTRODUCTION

The incidence of renal cell carcinoma (RCC) has increased significantly in the last 50 years[1]. In Europe on 2008 there were 88.400 new cases and 39.300 kidney cancer-related deaths per year[2]. Nephron sparing approaches (NSA) using minimal invasive techniques are highly aimed specially in small renal masses (SRM) defined as incidentally image-detected, contrast-enhancing renal tumors ≤ 4 cm in diameter[3]. While partial nephrectomy (PN) is the new gold standard of care for T1 RCC, there is a group of patients unfitted for surgery given their short life expectancy, co-morbidities or denial. In response to the need for NSA in patients unfitted for surgery there has been an increasing interest in percutaneous ablation techniques as radiofrequency ablation (RFA) and cryoablation (CA) among others.

RFA for the treatment of kidney tumors was initially described by Zlotta et al in 1997[4] and consist in transferring of alternating monopolar radiofrequency electrical current through needle electrodes into target tissue that results in ionic agitation, heating, and eventual desiccation with sub-sequent coagulative necrosis[5].

In the last years there is a growing knowledge about the influence of the tumor's anatomical complexity rather than just the diameter, in clinical outcomes when treatment for RCC is needed by NSA[6, 7]. In order to mesure and standardize that complexity, Kutikov and Uzzo developed the R.E.N.A.L. Nephrometry Score (RNS) in 2009[8] which assigns points considering size, location and deepness of renal tumors classifying complexity in low (4-6), medium (7-9) and high (10-12).

Contrast enhanced ultrasound (CEUS) is a real-time dynamic imaging technique that plays an important role in the management of patients treated with ablation for malignant tumors. Characterization of renal masses and cyst lesions is a well-established indication for CEUS[9]. In patients undergoing renal percutaneous tumor ablation, CEUS may be used as a pre-treatment evaluation, to improve lesion visualization in difficult cases, to guide the placement of ablation devices and to detect residual tumor either immediately or later after ablation[10, 11].

In the present study we analyzed the association among the RNS and clinical outcomes in patients with SRM treated with percutaneous RFA guided by CEUS.

Patients and methods

A retrospective study of consecutive patients who underwent percutaneous CEUS guided RFA performed in a single hospital in Barcelona, Spain between January 2005 and March 2015. Institutional review board ethics approval was obtained. Patients were initially evaluated by a urologist to determine and counsel about the best treatment strategy. If ablation is decided, the patient is referred to an interventional radiologist for feasibility assessment using CEUS. Patients lacking of digital images or other relevant data were excluded. Unless obtained beforehand, simultaneous renal mass biopsy was incorporated as routine practice, specially in later years. Biopsy was obtained at the same time during RFA ablation, so the final pathology report was revealed afterwards. We used a 15 cm electrode-needle Cool-Tip TM RF ablation system under conscious sedation plus local anesthesia. When a biopsy was performed, an 18 G needle was used. A bowel hydrodisection, transhepatic approach or a cold saline solution irrigation through an ureteral tube were performed if required. The technique used in our center was described in detail by Trilla et al in 2017[12]. Patients were evaluated in the urology clinic at 3, 6 and 12 months after treatment on the first year, then every 6 months for 4 years and yearly follow-up thereafter, assessing clinical condition, renal function and imaging including Computed Tomography Scan (CT) and/or CEUS.

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Outcomes and Definitions

Tumoral persistence was defined as the presence of a contrast enhanced nodule or soft tissue on treated area at the first 3 month control. In the absence of this findings the technique is considered as successful.

Oncological Outcomes:

Recurrence, defined as a contrast enhanced nodule or soft tissue on treated area after a negative first control.

Metastasis.

Cancer specific mortality (CSM) and all-cause mortality (ACM).

Complications according to the Clavien–Dindo system and length of hospital stay.

Functional results, using serum creatinine levels to calculate estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease formula. Pre-treatment and 12 months after levels were compared.

Statistical Analysis

Clinicopathological data and outcomes were analyzed using descriptive statistics. Outcomes and R.E.N.A.L. nephrometry scores were compared using Fisher's test for categorical variables and Mann Witney's and Wilcoxon's test for quantitative variables. Kaplan–Meier analyses was performed for overall, cancer-specific and local recurrence-free survival. Statistical significance was set at $p \leq 0.05$. SPSS software version 20.0 was used.

RESULTS

A total of 182 procedures were performed in a sample of 166 consecutive patients. We excluded 19 cases as we did not have the images to calculate the RNS, which could be obtained in 163 cases (89.5%) in 149 (89.8%) patients who were included in the analysis. Cohort characteristics are summarized in Table 1. The mean age was 71.7 years and 69.1% were men. Mean follow-up time was 33.3 months + 20.6 (2-102).

The mean RNS was 5.6 + 1.52 (4-11), 4.8 + 0.8 (4-6) in the low complexity group and 7.8 + 0.9 (7-11) in the medium complexity group (p= <0.001). Given that only one case was a highly complex RENAL, this single case was included in the average complexity group. Thus, 121 cases were of low complexity and 42 of medium complexity.

Tumoral Persistence

We identified 11 cases of tumor persistence (6.7%). The mean size of the tumors in the non-persistent cases was 2.6 cm whereas in those with persistence it was 3.3 cm (p = 0.01). The mean RNS was 5.58 in the cases with no persistence and of 5.73 in the cases with persistence (p = 0.788). Of the 121 cases of low complexity, 8 (6.6%) presented tumor persistence, whereas of the 42 cases of medium complexity, 3 (7.1%) presented tumor persistence (p = 0.57) (Table 2). The 11 cases of persistence were submitted to a second treatment, 9 of them through a second RFA and 2 cases with PN. 3 cases presented a relapse after re-treatment. 2 of them were treated with a new RFA while in one case a Radical Nephrectomy (RN) was performed.

Tumor Recurrence

We identified 15 (9.2%) cases of tumor recurrence, 8 biopsy proven RCC (7 re-treated, with RFA), 3 initially reported as benign (2 Oncocytomas, both re-retreated with RFA and one initially reported with no tumoral evidence, not re-treated) and 4 indeterminate (one re-treated with RN with final pathology diagnosis of RCC-clear cell, one re-treated with RFA and 2 not re-treated). No significance recurrence difference was observed among these 3 groups (p=0,344). Overall, 11 cases of recurrence were subjected to a second treatment, 10 RFA and 1 RN. In the remaining 4 cases, active surveillance was chosen considering patient general conditions and life expectancy. The mean size of the tumors in cases without recurrence was 2.6 cm +/- 0.1 (1.2-4.9) whereas in those with relapse it was 3.2 cm +/- 0.2 (1.9-4.7) (p = 0.02). The mean RNS was 5.57 +/- 0.1 (4-11) in the cases without recurrence and of 5.73 +/- 0.4 (4-9) in cases with recurrence (p = 0.804). Of the 121 cases of low complexity, 10 (8.3%) presented tumor recurrence, whereas of the 42 cases of medium complexity, 5 (11.9%) presented recurrence (p = 0.53). Of the 76 biopsy proven RCC cases, 8 (10.5%) cases of recurrence were observed, 5 in the low complexity group and 3 in the medium complexity group (p= 0.690). No significant differences of recurrence were observed among RCC subtypes (p= 0,927). Overall recurrence free survival (RFS) and biopsy proven RCC group RFS according to RNS are presented in Figure 1.

Metastasis

One case (1,3% of biopsy-proven RCC group) of nodal metastasis was identified at 12 months after the initial treatment in a patient who had presented tumor persistence that had been secondly treated by PN. The initial tumor was 2 cm with a RNS of 4. Biopsy of the tumor shown a clear cell RCC grade 2 of Fuhrman.

Mortality

In total, 19 deaths (11.7%), 14 (11.6%) in the low complexity group and 5 (11.9%) in the medium complexity group were identified (p= 1.0). No significant difference was observed in mortality regarding initial pathology report (7 RCC, 6 benign and 6 without biopsy, p=0,353). No cases of RCC-specific

mortality were identified. Overall survival according RNS is presented en figure 2.

Complications and Length of Stay

A total of 9 (5.5%) cases of complications were observed, with a distribution according to the RNS of 5 cases of 121 (4.3%) in the low complexity group and 4 of 42 (9.5%) cases in the medium complexity group (Table 2) (p = 0.23). In the uncomplicated group, the mean RNS was 5.5 + 0.12 (4-11), while in the group with complications the mean RNS was 6.33 + 0.5 (5-9) (p = 0.097). In the uncomplicated group the mean tumor diameter was 2.7 cm + 0.1 (1.2-4.9) whereas in the group with complications the mean tumor diameter was 3.3 cm + 0.5 (1.6-4.9) (p = 0.071). 5 complications were Clavien 1, 3 were Clavien 2 and 1 case was Clavien 3a (table 3). The mean length of stay was 1.5 days for the whole group, with a significant difference between low and medium complexity groups (1.3 vs 2.1 days, p= 0.02).

Renal Function

There were 8 patients who were on hemodialysis prior to ablation, so they were excluded from the analysis of renal function. During follow-up 7 patients underwent renal replacement therapy (RRT), 6 of them in a hemodialysis program while 1 patient received a renal transplant. Only 1 patient required RRT during the first year of follow-up. The mean preoperative eGFR was 66.6 +/- 25.2 (15.0-159.8), being in the low complexity group 64.3 +/- 2.6 (15.8-159.8) and in the medium complexity group 72.1 + 4.4 (15.0-114.3) (p = 0.298), while eGFR at 12 months post-ablation was 63.4 mL / min + 25.9 (8.6-138.8), being in the low complexity group 61.2 mL / min + 2.6 (8.6-138.8) and in the medium complexity group 69.2 + 4.6 (8.6-119.8) (p = 0.105). The mean difference between preoperative eGFR and estimated at 12 months was -3.08 mL / min + 13.3 (-49.4-34.1) and was significant (p = 0.008) however this variation did not show significant differences between the low and medium complexity groups (p = 0.936) (Table 2).

DISCUSSION

Since the first publication of the RNS, there have been many articles showing a significant association with several clinical outcomes[13] such as surgical approach[14], surgical complications[15], renal functional outcome[16], ischemia time[17], histology[18] and hospital stay[19] among other aspects, however there is still few evidence regarding percutaneous ablative techniques with contradictory results[20-23].

We observed a 6.7% of tumoral persistence, which is slightly higher than the 5.9% reported in the Systematic Review performed by Vollherbst et al[24] but lower than the 13% reported by Ptsuka et al[25]. We observed that tumor median size was significantly higher in patients with persistence. Using a CT guide, Ianuccilli et al studied 203 biopsy-proven percutaneous RFA finding that tumor size ≥3.5 cm confers a significant increased risk for residual tumor[26] whereas Wah et al found in multivariate logistic regression analysis of 200 percutaneous RFA that two independent predictors of successful RFA in a single setting were tumor size (<3 cm) and exophytic location[27]. The RNS was higher in in patients with tumoral persistence but this difference was not significative. Concordantly, the local failure ratio reported by Bhindi et al using CA (defined as failure of the ablation ice ball to extend beyond the tumour margin on monitoring CT imaging during the procedure) was neither associated to the RNS[23].

We found a recurrence rate of 9.2% (10.5% in biopsy proven cases) which is on the upper part of the interval observed in literature according Vollherbst et al Systematic review[24]. Tumoral size was significantly higher in patients with recurrence. The RNS was higher in patients with recurrence but this difference was not significative. These findings are not concordant with the results of Camacho et al who studied 101 biopsy proven SRMs treated with CA (54%) or RFA (46%) reporting a significant correlation between recurrence and a >8 RNS[28]. In another study performed by Schmit et al, 751 renal tumor were treated using percutaneous approach with CA (57%) or RFA (43%) and retrospectively categorized regarding the RNS, finding that mean RNS was 7.6 versus 6.9 in patients with or without treatment failure respectively (p=0.001). These differences may be explained by the lack of high complexity group in our study whereas the Camacho et al study had 61 low, 26 medium and 14 high patients regarding the RNS while Schmit et al study had 351, 330 and 70 low, medium and high complexity cases respectively. On the other hand, Maxwell et al studied 217 biopsy-proven SRMs treated mainly with CT guided percutaneous RFA reporting that maximum tumor diameter was the strongest predictor of local recurrence with a Harrell C index = 0.81 while RNS was found to be significantly predictive but showing poor performance with a Harrell C index = 0.68, limiting their overall utility in authors opinion[29]. Nor pathology report nor subtype of RCC were associated to recurrence nor mortality, which is consistent with previous research, finding that to 64-84% of SRM are indolent tumors and on the other hand, a significant proportion of patients with SRM who progress to metastatic cancer are not identified by current pathologic techniques. New technology in imaging and molecular analysis are currently in development to address this issue[30].

We had only one case of metastatic progression however it was in a patient who had a small (2 cm), low RNS and low Fuhrman's grade tumor which is concerning considering our current understanding of natural history of SRMs that rarely provoque metastatic disease when sized < 3cm[25]. Minardi et al studied 48 patients with a pT1a RCC treated with PN founding that distant metastatic disease occurred in 2.4% of patients with tumors <3 cm versus 8.4% of patients with tumors between 3.1 cm and 4 cm which is concordant with our results[31].

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We observed an ACM of 11.7% without statistical difference between low and medium RNS groups.

Our complication rate of 5.5% is within the range of 5.1-37% reported by Vollherbst et al Systematic review[24]. RNS and tumor's diameter were higher in the cases with complications, however no significant difference was found. Length of hospital stay was the only issue significantly associated with RNS. Tumoral diameter or size has been considered a significant factor influencing procedure's safety. In the Camacho et al study, a diameter > 2cm and a RNS > 8 were significantly correlated with the presence of complications while in the Schmit et al study, the RNS was found to be significantly higher (8.1 vs 6.8, p= 0.001) comparing patients with or without major complications. Again, the lack of a high complexity group in our study could explain these differences.

We observed a slightly but significant decrease of eGFR one year after the first RFA which reflects the fragility of this population. No significant difference was observed between RNS groups. Lucas et al

studied renal function in patients with RCC, finding that patients treated with RN were 34.3 times more likely to develop stage 3 chronic renal desease than patients treated with PN or percutaneous RFA[32]. In our study, one renal graft was successfully treated. Cool et al studied outcomes and graft viability after percutaneous RFA of 12 biopsy-proven RCC developing within renal transplant allografts. Authors report 100% of technical success and no recurrence nor progression after a mean follow-up of 54 months with no significant difference in eGFR previous and 6 months after the procedure[33].

According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines, the use of CEUS can be useful in the management of RCC patients undergoing ablation procedures due to the improved visualization of ambiguous tumors, the assessment of therapeutic efficacy within 24 h after ablation, the detection of unablated tumors and local tumor progression, and the ability to guide re-ablation of recurrent viable tissue[10]. In our study, all cases had a first evaluation by the same radiologist who performed the procedure assessing the reliability of the treatment. During the procedure, CEUS was used to guide the needle and to evaluate ablation's success in difficult cases. In our follow-up protocol CT scan and CEUS were used however we did not evaluate the concordance between CT and CEUS to detect recurrence.

Our study has several limitations. First of all, we performed a retrospective analysis reflecting the first ten years experience of a single hospital. Only in 79% of our treatments a biopsy sample was obtained as this was not part of our protocol in the first years. On the other hand, we had a lack of high complexity group according the RNS which could have influenced our results having a very homogeneous sample of patients that could prevented us from finding more significant outcomes.

In conclusion, percutaneous CEUS-RFA is a feasible technique with excellent functional and oncological outcomes and low rate of complications. The RNS was not associated with tumoral persistence, recurrence, cancer specific mortality, complications or renal function showing significance difference only in length of hospital stay between low and medium complexity groups.

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Attached tables:

1. CorrectedTables CEJU.docx
   Caption/remarks: *3 tables*

CorrectedTables CEJU.docx

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ATTACHED FIGURES

Figure 1. Recurrence-Free Survival (Kaplan-Meier) according RNS

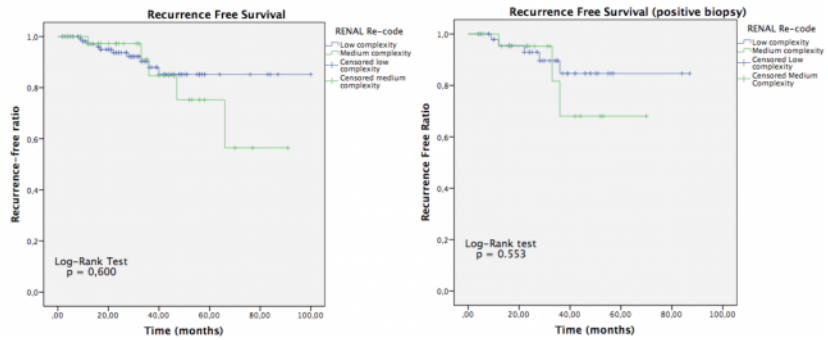
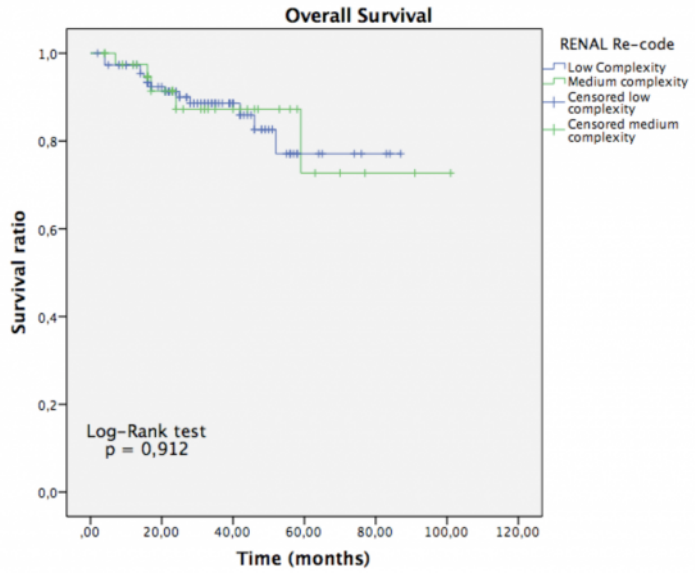


Figure1.png

Figure 2. Overall Survival according RNS



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