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# Radiofrequency Ablation in Renal Cell Cancer: Review

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## Abstract

Renal cell cancer is the most fatal urologic cancer which is diagnosed at the metastatic stage in 20-30%. Generally small-sized renal masses are defined as slowly progressing masses with a size of ≤4 cm and have a good prognosis. As a result of the improvements in USG, CT and MRI technologies, incidental tumor determination ratio has increased in course of time. The gold standard treatment for small-sized renal masses is open/laparoscopic/robotic partial nephrectomy. RFA is a minimal invasive therapy method which is a good alternative to surgery in elder comorbid patients or the patients with genetic predisposition for multiple tumors or patients with bilateral tumors or patients with a solitary kidney. In this review we want to discuss technique, overall outcomes and complications of RFA and compare its efficacy with surgery and cryoablation according to the current literature.

RFA is a good alternative treatment method for the RCC's smaller than 4 cm with an oncologic efficiency closer to nephron protecting surgery and with lower complication ratios. More prospective randomized controlled studies are required in order to reveal the efficiency difference between cryoablation and RFA. We consider that in order to decrease the complication rates and to increase efficiency, making a good preoperative assessment and avoidance of RFA in central, renal tumors larger than 4 cm will be a rationalist approach.

**Keywords: Radiofrequency ablation; Kidney; Renal cell carcinoma; Complications**

## Introduction

Renal cell cancer is the most fatal urologic cancer [1] which is diagnosed at the metastatic stage in 20-30% [2]. As a result of the improvements in USG, CT and MRI technologies in course of time; incidental tumor determination ratio that was 10% in 1970s [3] has increased to 61% at the end of 1990s [4]. Thus today, we encounter small-sized renal masses more frequently when compared to the past. Generally small-sized renal masses are defined as slowly progressing masses with a size of ≤4 cm and have a good prognosis [5]. The gold standard treatment for small-sized renal masses is open/laparoscopic/robotic partial nephrectomy [6]. Minimal invasive therapies with low complications rates can be applied to; elder comorbid patients or the patients with genetic predisposition for multiple tumors or patients with bilateral tumors or patients with a solitary kidney. Radiofrequency ablation, cryoablation, microwave ablation, stereotactic radiosurgery, laser ablation and high-intensity focused US ablation take place among the minimal invasive treatment approaches. Most of these methods are at experimental stage but cryoablation and RFA are intensely used in clinical practice [6].

RFA is an ablation treatment that is approved by FDA (US Food and Drug Association) regarding to the treatment of soft tissue tumors. It is used in the treatment of liver, lung and bone tumors. In 1997, after Zlotta et al. [7] has firstly used RFA in the treatment of RCC, RFA has found a wide clinical usage area in the treatment of small-sized renal masses. In this review, we want to investigate the oncological efficiency and reliability of RFA in ablative treatment of small kidney tumors with the current literature.

## Technique and Mechanism of Action

Although RFA (Radiofrequency ablation) can be applied percutaneously and laparoscopically, current literature belongs mostly to the percutaneous technique. Percutaneous approach is generally applied under general anesthesia or sedation but general anesthesia is preferred in laparoscopic technique. The selection of technique depends on the operator and it seems that percutaneous or retroperitoneoscopic approach is more suitable for the treatment of lateral and posterior located

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tumors and laparoscopic approach is more suitable for the treatment of anterior-located tumors [8]. Preoperative routine laboratory examinations should include renal function tests and coagulation parameters. INR (International normalized ratio) should be under 1.5, partial thromboplastin time should be within normal limits and thrombocyte count should be over 50.000/µL. If coagulopathy is present, fresh frozen plasma and thrombocyte transfusion should be performed. Independent from the laparoscopic or percutaneous approach, it is recommended to conduct a biopsy on the tumor before the process [1]. In order to determine the collecting duct system and ureteral injuries; preoperative ureter catheter can be applied and via continuous cold fluid infusion during the operation, urinary system can be protected from thermal damage [9]. In order to avoid thermal damage-related complications; the location of the tumor and its proximity to the ureter, intestine and nerves should be preoperative assessed in detail [10]. In preoperative planning, tumor characteristics can be defined via simple algorithms such as ABLATE [11], R.E.N.A.L nephrometry [12]. Placing of the probes is performed under the guidance of USG and CT. Until now, there is no sufficient evidence about the superiority of a method than the other one. In radiofrequency ablation, high-frequency (375-400 Khz) alternative electric current is transferred to the tissue via a probe and causes mobilization and friction of the tissue ions and this causes warm-up on the tissue. In early period over 50°C with 4-6 minutes of warm-up (within two days); irreversible cell damage occurs as a result of protein denaturation, membrane catabolism and cell vaporization. In the late period (after third day), fibrotic scar occurs as a result of the development of coagulation necrosis [13]. Temperatures over 105°C cause gas formation and this may disrupt RF current. Thus in RF ablation, the target is to keep the temperature on the tumor tissue between 50°C and 100° C [14]. Ablation should be targeted till 0.5-1 cm beyond the deepest point of the tumor, because in a report, live tumor cells are found periphery of the tumor in a patient to whom RFA is applied [15]. Besides conventional ablation, there are also researches about ablation via multiple electrodes. This system permits the usage of up to 3 electrodes, power varies between the electrodes respectively and thus a larger ablative zone is formed via thermal synergy [16]. System is new and although phase 2 studies are encouraging, the results should be supported via new studies [17]. It is recommended to apply CT/MRI imaging subsequent to RFA after 1-3 months, perform 3 scans in 6-month intervals and then 1 interval per year [18]. After the first scan (postoperative 1-3 months), contrast-enhancing lesions are accepted as insufficient ablation and re-application of RFA may be required. In the study of Gervais et al. [19] consisting of 100 patients, low tumor size ($p < 0.0001$) and non-central location ($p = 0.0049$) for complete necrosis after a single ablation are determined as independent predictor factors.

## Oncologic and Overall Outcomes

There are numerous studies in the literature regarding to the long-term oncologic efficiency of RFA application in small-sized renal masses. Levinson et al. [20] have shared the long-term follow-up results of RFA in small renal masses in 2008. In this study, in a follow-up of mean 57.4 months, disease-specific, metastasis-free, recurrence-free and general survival ratios are reported as %100, %100, %79.9 and %58.3 respectively. In the same study, creatinine value decrease is measured as 0.15 (p=0.06). In 2010, Ferakis et al. [21] have published 61.2 months average follow-up results of CT-guided percutaneous radiofrequency ablation in 39 renal tumors smaller than 7.5 cm. while the first ablation success ratio is 90%, complete ablation ratio after repeating the treatment has reached to 97%. In a 5-year follow-up; recurrence ratio is found as 10.4%. For recurrence, various parameters are examined via multivariate analysis and the tumor size over 4 cm is defined as a risk factor (P<0.01, relative risk [RR] =3.31). Zagoria et al. [22] has determined recurrence in 5 of 48 RCC which percutaneous RFA is applied (12%). While median index size is 5.2 cm in recurrent tumors (interquartile range [IQR]: 4-5.3), median index size in the tumors with no local recurrence is observed as 2.2 cm (IQR: 1.7-3.1, $p$=0.0014). In a study with median follow-up of 54 months for RFA-applied 159 renal tumors; 3 and 5-year disease-free survival are observed as 92% and 91% respectively. In the same study, local recurrence is directly found as related to size [23]. In 2012, Psutka et al. [24] have applied RFA to 143 T1a and 42 T1b RCC and compared their oncologic results. When the results are inspected, 5-year survival as recurrence-free, metastasis-free survival, cancer specific survival, disease-free survival and general survival ratios are found worse in T1b RCC group when compared to T1a group. Lorber et al. [25] have published the long-term results of percutaneous or laparoscopic RFA-applied patients by using a real-time thermometer with the aim of applying appropriate heat to 53 renal masses in 2014. In a mean follow-up period of 65.6 months; local recurrence is observed in 4 (7.5%) patients and distant metastasis without local recurrence is observed in 1 patient. 5-year overall survival of these patients is informed as 98%, cancer-specific survival as 100% and recurrence-free survival as 92.5%.

In a study comparing oncologic results of RFA and partial nephrectomy which is having a follow-up period of more than 6 years; despite RFA group's comorbidities are more and they are older, the survival ratios of the patients in RFA group are found similar to the PN patients [26]. In this study, RFA vs. PN 5-year general survival, cancer-specific survival, disease-free survival, local recurrence free survival, metastasis free survival was found 97.2% vs. 100%(p=0.31), 97.2% vs. 100%(p=0.31), 89.2% vs. 89.2%(p=0.78), 91.7% vs. 94.6%(p=0.96), and 97.2% vs. 91.8%(p=0.35), respectively. In another study, RFA and PN are compared in 90 T1a RCC patients and 5-year oncologic results were found similar [27]. Besides intraoperative blood loss is higher (p <0.001), operation period is longer (P <0.001) and in the final follow-up, GFR value has decreased more (p=0.005) in PN group. In terms of major complications (Clavien system ≥IIIa), no difference is observed between two groups. While assessing the results of this study, it should be considered that tumor sizes of PN group are bigger. In the study of Faddegon et al. [28] published in 2013; RFA-applied 142 RCC patients and PN-applied 205 RCC patients are compared in terms of renal functions and on the 5th year and it is shown that 85.4% of RFA-applied patients and 82.1% of PN-applied patients have continued their lives without Chronic Kidney Disease stage progression, however this difference cannot reach to a statistical significance level (p=0.06). In the study of Thompson et al. [29] examining 1424 T1a RCC patients, PN is applied to 1057 patients, RFA is applied to 180 patients and cryoablation is applied to 187 patients. When the patient groups are compared, similar survival ratios are observed among 3 groups without local recurrence (p=0.49) however metastasis-free survival was found better in PN (p=0.005) and cryoablation (p=0.021) groups when compared to RFA group. Although general survival is found higher in PN group, it is suggested that this finding has occurred due to the young age of PN patients and their lower Charlson scores. In the study of Takaki et al. [30] published in 2014, RFA and PN were compared in the treatment of T1b renal tumors. On the 1st post-treatment month, GFR (Glomerular Filtration Rate) reduction ratio is statistically significantly higher in

the PN group when compared to the RFA group (*P*=0.001). Besides no significant difference is found between major (*p*= 0.61) and minor (*P* = 0.12) complications between two groups. Despite general survival ratios are better in PN group (p=0.009), higher age and ASA (American Society of Anesthesiologists) scores of RFA group requires a closer approach to this finding. In the same study, the disease-free survival ratios are found similar in both groups (p=0.99). In the study of Whitson et al. [31] in which they have examined ablation-applied (cryoablation, RFA or NOS) or PN-applied 8818 T1a RCC patients via the Surveillance Epidemiology and End Results (SEER) database, it is found that RFA has twice increased RCC mortality risk when compared to PN (hazard ratio 1.9, 95% confidence interval 1.1–3.3, p=0.02). 5-year disease-free survival ratios are observed as 98.3% in PN group and as 96.6% in ablation group. When the details of this wide study are examined, it is seen that the number of RFA-applied patients is 219 and 50% of these patients have no histologic data. Thus these results should be carefully considered. Again in another study performed by examining the SEER database data, regarding to renal masses smaller than 7 cm, PN (n=4402), Radical nephrectomy (n=10.165) and RFA/Cryoablation (n: 578) are compared and 1 and 2-year cancer-specific survival (CSS) are found as 99.4% and 98.0% for TA (termal ablation)group and as 99.6% and 99.3% for PN group and as 98.9% and 98.0% for Radical nephrectomy group. In univariate analysis, CSS is found significantly lower in TA group when compared to PN group. (1.6% vs. 0.7%; *P* =0.025). However, when the TA and PN patients are compared in terms of age, gender, tumor size, race, geographic location, no difference is found. (hazard ratio 0.6, 95% CI 0.28–1.28; *P* =0.2) [32]. In this study, no subgroup analysis is done for the tumors smaller than 4 cm. In a meta-analysis consisting of 6471 small-sized renal masses examining 99 studies of Kunkle et al. [33] when compared to PN, higher local progression ratios in cryoablation (RR = 7.45) and RFA (RR = 18.23) are observed. However, no difference is observed between the groups in terms of metastatic progression risk. In the meta-analysis of Katsanos et al. [34] performed in 2014 by scanning the PubMed, EMBASE, AMED, database, includes the studies with 6 or more stars on Newcastle-Ottawa Scale, thermal ablation (RFA or microwave) was compared to PN in small-sized renal masses in 587 patients. In this study, general complication ratios were found lower in ablation group (7.4 vs. 11 %; RR: 0.55, 95 % confidence interval [CI]: 0.31–0.97, p=0.04), besides postoperative GFR reduction was found higher in nephrectomy group (mean difference: -14.6 ml/min/1.73 m2, 95 % CI: -27.96 to -1.23, p = 0.03). Local recurrence ratios (3.6 vs. 3.6 %; RR: 0.92, 95 % CI: 0.4–2.14, p = 0.79) and disease-free survival ratios are found similar (HR: 1.04, 95 % CI: 0.48–2.24, p = 0.92) in both groups. As a result, when the literature is examined, it is seen that radiofrequency ablation has lower complication ratios than partial nephrectomy in the treatment of renal tumors smaller than 4 cm and has a close-may be equal-oncologic efficiency with nephrectomy. Again while the literature is being examined, it is observed that mostly the retrospective data is examined and there are some problems regarding to the patient selection (differences in age, comorbidity and tumor size between the groups etc.). In order to obtain more exact conclusions, more prospective randomized controlled studies are required.

In the small-size RCC treatment; the evidences regarding to the efficiency of cryoablation increase every passing day like RFA. Due to being a minimal invasive treatment and having low complication and high efficiency, cryoablation continues its claim of being an alternative for PN like RFA. Thus the number of studies comparing the efficiency of both minimal invasive treatments increases day by day. Cryoablation and RFA have some technical superiority than each other. In central renal tumors, efficiency of RFA should be elaborated. Gervais et al. [19] have shown that RFA has a local recurrence increase in central renal tumors. Similarly, Gupta et al. [35] have revealed that in central renal tumors treated by RFA, 4 times increased insufficient treatment risk is present when compared to the non-central tumors. Takaki et al. [36] have shown that local control in central tumors (67%) is lower than the non-central tumors (96%). Besides cryoablation can be used safely and efficiently in the treatment of central renal tumors [37]. During RFA procedure, coagulation of puncture tract with probe change makes RFA attractive in the patients with high bleeding risk, than cryoablation [38]. When the studies comparing the efficiencies of RFA and cryoablation are compared, various results can be observed in the literature.

In the study of Atwell et al. [39], cryoablation is applied for 189 renal tumors smaller than 3 cm and RFA is applied for 256 renal tumors. 1, 3and 5-year recurrence-free survival are observed as 100%, 98.1%, and 98.1% in RFA group and as 97.3%, 90.6% and 90.6% in cryoablation group however this difference can't reach to statistical significance (*p*=0.09). Major complications are found as 4.3% after RFA and as 4.5% after cryoablation and no difference is observed (p=0.91). The point to consider while assessing the results of this study is that the tumors in cryoablation group are bigger than the RFA group (p<0.001). In 2011, Pirasteh et al. [40] have compared cryoablation and RFA in small-sized renal tumors in 111 patients. In this study, local recurrence is observed as 11% in RFA group and as 7% in cryoablation group and this difference has not reached to statistical significance (p=0.60). In the first meta-analyses published in 2008 comparing the efficiencies of cryoablation and RFA [33,41], it is found that cryoablation is superior in the treatment of small-sized renal tumors in terms of oncologic means when compared to RFA. In the meta-analysis published by Kunkle and Uzzo [41], 1375 renal tumors treated via RFA or cryoablation are examined and local tumor progression ratios are found higher than cryoablation (12.9% vs. 5.2%; P< .0001). Although metastasis develops less in cryoablation patients (1%) than the RFA (2.5%) patients, this difference cannot reach to statistical significance (p=0.06). Also recurrent ablation has occurred at a higher ratio in RFA group when compared to the cryoablation group (8.5% vs. 1.3%; P< .0001). In the meta-analysis of AUA (American Urological Association) performed in 2009 [42] local recurrence-free survival ratios for RFA (85.6%) and cryoablation (87.2%) are found similar and these are observed as lower than the surgical methods (PN/Radical nephrectomy). While assessing these findings, it should be considered that failure after the first ablation was accepted as local recurrence in this study. However, it is known that most of the patients can continue their lives as recurrence-free with secondary ablation. Besides the success of ablation treatments is only assessed by local recurrence in this study. Unlike these early-period meta-analyses, in the meta-analysis published by El Dib et al. [43] in 2013, 457 cryoablation cases are compared to 426 RFA cases and clinical efficiency is measured by using the below mentioned parameters: cancer specific survival rate, radiographic success, no evidence of local tumor progression or distant metastases. The pooled proportion of clinical efficacy calculated as 89% in cryoablation group and as 90% in RFA group. Besides no difference is observed between cryoablation and RFA groups in terms of complications. Except all this information, in the studies comparing RFA and cryoablation in the literature until now, the minority of prospective/randomized data

and the suboptimal design of the studies (ex: ages of the patients and the differences in the tumor sizes) draw attention. The data acquired until now are far away from obtaining exact conclusions.

Although RFA is generally observed as safer than surgical methods, when the current literature is examined in terms of the complications of RFA, a wide clinical picture is encountered (Hematuria, flank bruise, paresthesia and pain, perinephric hematoma, ileus, urinary retention, urinoma, ureteral stricture, tract abscess, hemorrhage, urinary fistula, neuropathic pain, atrial fibrillation, pneumonia etc.) In order to avoid complications, it is required to assess the surrounding tissues via imaging methods in detail before RFA. Hemorrhagic complication rates after RFA are similar to percutaneous renal biopsy and generally they are recovered via conservative follow-up. Filling the tract with hemostatic agents generally minimizes this complication [44]. In order to both avoiding from hemorrhagic complications and preventing urinary system injuries; avoidance from RFA in central tumors seems to be a rationalist approach. In order to avoid an intestinal injury, which is one of the most threatening complications, it is recommended to use laparoscopic RFA application in the patients with no suitable intestinal anatomy in preoperative prone CT [45]. Alternatively, for safety purposes, saline, $C0_2$ or water can be applied adjacent to the kidney in order to remove the intestine minimum 2 cm away from the kidney before the operation [46].

## Conclusion

RFA is a good alternative treatment method for the RCC's smaller than 4 cm with an oncologic efficiency closer to nephron protecting surgery and with lower complication ratios. More prospective randomized controlled studies are required in order to reveal the efficiency difference between cryoablation and RFA. We consider that in order to decrease the complication rates and to increase efficiency, making a good preoperative assessment and avoidance of RFA in central, renal tumors larger than 4 cm will be a rationalist approach.

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