Minimal Invasive Management of Small Renal Masses: State of Art and New Trends

Küçük Renal Kitlelerin Minimal İnvazif Yönetimi: Son Gelişmeler ve Yeni Trendler

Küçük Renal Kitlelerin Minimal İnvazif Yönetimi / Minimal Invasive Management of Small Renal Masses

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Özet

Ultrasonografi, bilgisayarlı tomografi ve manyetik rezonans görüntüleme gibi radyolojik görüntüleme yöntemlerinin yaygın kullanımı ile birlikte özellikle 2 cm'den küçük, klinik olarak lokalize böbrek tümörlerinin insidansında göze çarpan bir artış olmuştur. Dahası, bu lezyonların kesin patoloji sonuçları %30'lara kadar iyi huyludur. Probların gelişmesi ve eş zamanlı görüntüleme yeteneği gibi sürekli yenilikler ile birlikte ablasyon tekniklerinin (radyofrekans ablasyon [RFA], krioablasyon [CA], yüksek yoğunlukla odaklanmış ultrasonografi [HIFU], microwave ablasyon [MWA]) gelişmesi özellikle T1 renal tümörlerin tedavisinde bu tekniklere olan ilgiyi arttırmıştır. RFA ve CA'nın nefrektomi ile karşılaştırıldığında benzer kanser-spesifik sağkalım, hastalıksız sağkalım, nükssüz sağkalım ve genel sağkalım oranları vardır. MWA ve HIFU düşük hasta sayıları ve yetersiz klinik deneyim ile hala deneyseldir. Minimal invazif teknikler pek çok komorbiditesi ile yüksek cerrahi ve anestezik riske sahip, VHL gibi sistemik hastalıklara bağlı birçok tümörü olan ya da cerrahiye gitmek istemeyen hastalar için uygun bir teknik olabilir. Özellikle rölatif kısa yaşam beklentisi ve düşük performans durumlu yaşlı hastalar bu işlemler için iyi birer aday olabilirler.

Anahtar Kelimeler

Böbrek Tümörü; RFA; HIFU; MWA

Abstract

With the widespread use of abdominal imaging modalities such as ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI), there has been a pronounced increase in the incidence of renal tumors especially clinically localized, small < 2 cm ones. Moreover the final pathology of these lesions is benign up to 30%. The development of ablation techniques (radiofrequency ablation, cryoablation, high-intensity focused ultrasound and microwave ablation) with continuous innovations such as refinement of probes and real-time imaging capabilities has pioneered the great interest in these techniques, especially for the treatment of T1 renal malignancies. RFA and CA have similar cancer specific survival, disease-free survival, recurrence free survival and overall survival rates compared to nephrectomy. MWA and HIFU remain still experimental due to low patient volume and insufficient clinical experience. Minimal invasive techniques can be a feasible treatment alternative for patients who have high surgical and anesthetic risk with multiple comorbidities, have multiple tumors due to a systemic disease like VHL or do not want to undergo extirpative surgery. Especially elderly patients can be good candidates for these procedures with their relatively short life expectance and impaired performance status.

Keywords

Renal Masses; RFA; HIFU; MWA

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Introduction

With the widespread use of abdominal imaging modalities such as ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI), there has been a pronounced increase in the incidence of renal tumors especially clinically localized, small < 2 cm ones [1]. It is estimated that more than 50% of renal cell carcinomas (RCCs) are being identified incidentally [2]. This exaggerated utilization of modern technology has led to the alteration of clinical landscape of renal tumors. At the present time, majority of renal tumors are detected incidentally with small dimensions (<4cm), low grade and low malignant potential. Moreover the final pathology of these lesions is benign up to 30% [3].

The surgical management of RCC has evolved impressively subsequent to description of radical nephrectomy (RN) and ipsilateral adrenalectomy as gold standard treatment in 1969 [4]. The data supporting that surgically induced chronic kidney disease may increase cardiovascular and metabolic risk factors has led a shift toward nephron preserving treatment options [5]. Currently, partial nephrectomy (PN) has became the gold standard for the management of small renal masses (SRMs) because it preserves the normal renal parenchymal tissue and has similar oncologic outcomes to radical nephrectomy [6]. While PN has similar oncologic outcomes to RN, it is related with increased complications [5]. Another management choice in SRMs is active surveillance (AC). AC surveillance is postulated as an appropriate initial strategy for SRMs. It is especially convenient for elder patients with multiple or serious comorbidities thus unfit for surgery [7].

Minimal invasive treatment modalities like thermal ablations (cryotherapy or radiofrequency ablation) and high intensity focused ultrasound (HIFU) can be a good choice for those patients who are unsuitable for or not willing to undergo extirpative surgery, elderly or have multiple tumors due to systemic diseases like Von-Hippel Lindau (VHL) disease. The development of ablation techniques with continuous innovations such as refinement of probes and real-time imaging capabilities has pioneered the great interest in these techniques, especially for the treatment of T1 renal malignancies. Ablation procedures also have some superiority in terms of cost compared to both open and radical nephrectomy [8].

On the other hand, the maximum tumor size for such ablative techniques still remains controversial. While EAU guidelines restricts it use with tumors smaller than 3 cm some studies have reported success in pT1b (4-7 cm) tumors [3].

The purpose of the following section is to overview the current literature to provide the reader a point-view about most often applied ablative procedures.

Radiofrequency Ablation (RFA) of Renal Tumors

RFA or radio thermal ablation is a tissue-destruction technique, which uses thermal energy produced by alternating high-frequency electric current between 100-500 kHz. The current reaching the tissue via needle electrode causes the resistive heating of adjacent tissue known as Joule effect. Alteration of tertiary structure of intracellular protein occurs at 60° C which causes the denaturation of collagen and lipid bilayer damage. Thermal coagulation starts at 70° C while the drying of the tissues takes places at about 100° C. Higher temperatures are not suggested due to increase in impedance and diminish in the efficacy of the treatment caused by the tissue charring [9]. RFA can be performed either laparoscopic (L/S) or percutaneous.

RFA has been widely accepted as an affective nephron-sparing procedure in the management of small RCCs. The AUA guidelines recommended RFA as a treatment option especially for clinical T1a RCC patients. Multiple retrospective studies have demonstrated that RFA has a similar cancer-specific survival (CSS) and disease-free survival (DFS) rates compared to nephrectomy in clinical T1a RCCs [10].

Chang et al. conducted a study with 268 patients providing us information on perioperative and long-term outcomes of RFA and PN. As perioperative outcomes they found larger estimated blood loss (243.3 ±284.8 mL vs. 74.8± 50.8 mL, P < 0.001), longer operative time (171.5± 32.4 min vs. 132.6± 24.9 min, P < 0.001) and larger GFR percentage change in PN patients. There was no statistically significant difference between the two groups regarding to hospital stay and major complications (Clavien system: ≥ IIIa). After minimum 5 years of follow up no significant difference was found in the oncologic outcomes between the two groups as having similar 5-year overall survival (OS) and 5-year CSS [10].

İn another study comparing local recurrence-free survival (LRFS), metastases-free survival (MFS) and OS among patients treated with PN, percutaneous RFA and percutaneous cryoablation (PCA) demonstrated similar local control among the three groups, inferior MFS for RFA and superior OS for PN [11].

Young et al. reported favorable results for L/S RFA for T1b renal tumors. They performed L/S RFA on 51 patients with a 5.1±0.6 cm mean tumor size. The initial ablation success rate was 90.2%. They reported the 3-year disease-free survival as 84.7%. Mild complications like postoperative fever and perinephric hematoma was seen in 6 patients. No significant difference has found between pre and post RFA estimated GFR [12].

In their retrospective study conducted with 165 patients, Wah et al. performed 200 RFA for renal tumors with a mean size of 2.9 (1-5.6) cm. The patients had 46.1 months of mean follow-up. All tumors <3 cm has ablated completely (133/133), 1 patient through 63 with 3-5 cm tumor and 2 of 4 with >5 cm tumor has ablated incompletely with a single RFA session. The independent predictors of successful RFA in a single session were tumor size and exophytic location. They found a significant difference between the GFR measurements before and after RFA, where the GFR was higher before treatment (54.7 vs. 52.7-mL/min/1.73 m2). 10 major complications were reported as 6 ureteric injuries, 1 calyceal-cutaneous fistula, 1 acute tubular necrosis and 2 abscesses. The OS, 5-year CSS, LRFS and MFS rates were 75.8%, 97.9%, 93.5% and 87.7% respectively [13].

Takaki et al. compared RFA to radical nephrectomy for T1b RCC. They have found OS rate significantly lower in RFA group than RN group (48% vs. 97% at 10 years). RCC-related survival rate and DFS rate was comparable between the two groups. The percentage of decrease in the GFR was significantly higher in the RN group than in the RFA group (32.3% ±20.8 vs. 12.5%± 23.4). Major complication rates found similar between the two groups [14].

Miller et al. stated that percutaneous thermal ablation both RFA and CA, is safe and effective in the management of octogenarian and nonagenarian patients with clinical T1a tumors [15].

A recent paper by Ma et al. [16] showed durable oncological and functional outcomes for T1a tumor patients who underwent RFA. The 5- and 10-year recurrence free survival (RFS) rate was reported 94.2%.

Some researchers focused on the radiation exposure and its effects on life expectancy (LE) during the CT-guided ablation of renal masses and their follow-up. Eisenger et al. found that cumulative RFA radiation exposures (up to 305.2 mSv for one session plus surveillance) exceed from surgery (up to 87.2 mSv). They estimated that increased LE loss associated with RFA compared to surgery, related to differences in radiation exposure is 1-2 weeks in 65-year old patients. They emphasize that this value increases with decreasing age thus dose-reduction strategies must take into consideration in young patients especially in post-RFA follow-up CT scans [17].

Cryoablation (CA) of Renal Tumors

Cryoablation directly damages tissue by producing intra and extracellular ice, which disrupts the cell membrane. This damage leads to coagulation necrosis, fibrosis and scarring over the time. Temperatures between -40 and -20 C are ideal for the procedure. These low temperatures also leads to a indirect tumor killing due to microvasculature thrombosis [18]. Cryoablation of renal tumors can be performed either laparoscopic or percutaneous. Many studies have evaluated the outcomes of those CA techniques.

Larcher et al. stated the long-term oncologic outcomes of laparoscopic cryoablation (LCA) as primary treatment for cT1a RCC in 174 patients. In that study median tumor size was 20 mm and median follow-up was 48 months. Local recurrence was recorded in 4 biopsy-proven RCC patients. They reported the 10-year RFS rate as 95% and the 10-year systemic progression-free survival (PFS) rate as 100% [19].

Babaian et al. reported clinical outcomes of 114 patients who underwent cryoablation for small renal masses. 72 tumors were biopsy-proven RCC, 18 benign tumors (BT= angiomyolipoma or oncocytoma) and the remaining 27 were non-diagnostic (ND). 9 patients (12.5%) in biopsy=proven RCC group developed recurrent disease. The 2-year and 5-year RFS rates for this group were 90.2% and 81.2%, respectively as well as the RFS rate for the remaining two groups was 100% [20].

In a recent study conducted by Lai et al. , feasibility of CT-guided percutaneous cryoablation (PCA) in renal tumors was investigated. 7 patients experienced (23.3%) complications < Grade 4 based on Clavien-Dindo classification. They noted incomplete ablation in 2 patients and local tumor recurrence in another 2. Local tumor control was reported as 86.4% [21].

Theoretical advantages of laparoscopic approach are insertion of probes under direct visualization and treatment of anterior tumors. On the other hand percutaneous approach presents shorter recovery time, ability to be performed on an outpatient basis and avoidance of general anesthetıc. Several studies compared percutaneous with laparoscopic cryoablation. Zargar et al. analyzed 275 patients who underwent LCA and 137 patients who underwent PCA for small renal masses. They found that the overall and major complications were similar. 36 patients (13.1%) in LCA group and 20 patients (14.6%) in PCA group reported to have a local recurrence. They found no significant difference in OS and RFS at 5-years between the 2 groups. Oncologic outcomes were found equivalent between the 2 techniques. Also there was no significant difference in median GFR preservation between LCA and PCA [22].

One meta-analysis compared LCA to laparoscopic PN (LPN) for the treatment of SRMs. This analysis included 555 cases and 642 controls. They found LCA was associated with shorter operative time, less blood loss and major complications on the other hand LPN is related with significantly lower local recurrence and distant metastasis rate [23].

In another systematic review and meta-analysis compared LCA to LPN showed similar results. LCA was associated with significantly shorter operative time (weighted mean difference [WMD] 35.45 minutes), lower estimated blood loss (WMD 130.11 ml), shorter length of hospital stay (WMD 1.22 days) and a lower risk of total and urological complications. At the same time LCA represents a sıgnıfıcantly rısk of local and metastatic tumor progression [24].

Schmit et al. focused on complications of renal CA. They found that maximal tumor diameter and central tumor location, prior myocardial infarction, complicated diabetes mellitus were significantly associated with major complications [25].

Microwave Thermal Ablation (MWA)

MWA is an actual ablative therapy used for soft tissue destruction. Microwave energy applied into the tissue via an antenna. Microwave energy constitutes a electromagnetic field, causes high-frequency ion vibration and intermolecular collision that creates frictional heat, by this way leads to high temperatures as well as coagulation necrosis [26]. In addition to its similarity to RFA it has some superiority such as higher intratumoral temperatures, larger ablation zone, less treatment time, less dependence on electrical conductivities of tissue and more entire tumor destruction [26, 27]. It could be considered in treating small SRM percutaneously or laparoscopically.

Bai et al. reported results of 22 patients with cT1a patients who underwent retroperitoneoscopic MWA. The mean tumor size was 2.8 cm. Mean ablation time for per tumor was about 12.4 minutes. Mean estimated blood loss was 72 ml and the mean operative time was 99 minutes. No intraoperative complications were occurred. There was no significant change in creatinine level and glomerular filtration rate after the treatment or during follow-up. Successful MWA was documented in 17 (94.4%) of 18 tumors (Table 1) [26] .

Carrafiello et al. conducted a retrospective observational study with 12 patients who had RCCs smaller than 3 cm and treated with percutaneous MWA. They reported technical success rate and clinical effectiveness as 100%. No tumor recurrence was seen on follow-up. Also no major complications reported during or shortly after MWA. The ablation volume ranged between 10.2 and 25.1 cm3 [28].

In contrast Castle et al. found poor oncologic outcomes with a significant complication rate at an intermediate term follow up in their percutaneous MWA series. The recurrence rate of 10 patients with a mean tumor size of 3.65 cm who underwent percutaneous MWA as 38% and the intraoperative and postoperative complication rate was 20% and 40%, respectively [29].

Yu et al. reported the outcomes of 46 patients with 49 RCC who underwent US guided percutaneous MWA. Complete ablation rate was 98% and metastasis-free and cancer specific survival rates were 100% [30]. In another study Yu et al compared 65 patients who underwent MWA and 98 patıents who underwent open RN for SRM. They found MWA group overall survival significantly lower than open RN, 67.3% and 97.8%, respectively. But 5-year RCC-related survival rates for MWA and open RN were comparable, 97.1% and 97.8, respectively [27].

Moreland et al. evaluated 53 consecutive patients with biopsy-proven RCC≤ 4 cm who were treated with percutaneous MWA. The mean tumor size was 2.6 cm. There was significant difference between preoperative and postoperative GFRs. Six low-grade (Clavien 1-2) complications was documented. With

Table 1. The Outcomes of Recently Published Studies on Minimal Invasive Treatment Modalities

	Authors		References	No. Patients	No. Tumors	Mean/Median follow-up	İnitial/Technical success (%)	RFS (%)	CSS (%)	DFS (%)	OS (%)
RFA	Chang, et al		J Endourol 2015.	45	Na	67.6±6.0	Na	95.4	95.6	86.7	90.2
	Yang, et al		J Endourol 2014	51	Na	31.5	90.2	Na	Na	84.7 (3yr)	Na
	Wah, et al		BJU Int 2014;	165	200	47.6	95.5	93.5	97.9 (5yr)	Na	75.8 (5yr)
	Takaki, et al		Radiology 2014	21	Na	46.1±32.1	81	Na	94 (10yr)	88 (10yr)	48 (10yr)
	Ma, et al		BJU Int 2014;	52	58	60	100	94.2	100	Na	95.7
CA	Larcher, et al		Urol Oncol 2015	109 *	Na	48	98	95	100	90 (5yr)	95(5yr)
	Babaian, et al		Urology 2015	72*	Na	26.5	98.6	81.2(5yr)	Na	Na	Na
	Lai, et al		J Chin Med Assoc 2015.	30	32	15.2	91*	90.9 (6mth)	Na	80.9	95.2
	Zargar, et al	LCA	Urology 2015.	275	Na	52.9	93.1	79(5yr)	Na	Na	89(5yr)
		PCA		173	Na	37.8	93.4	80(5yr)	Na	Na	82(5yr)
MWA	Bai, et al		J Endourol 2010	22	23	20**	94.4**	Na	Na	Na	Na
	Yu, et al		Radiology 2014	65	69	20.3	85.5	Na	97.8	Na	67.3(5yr)
	Carrafiello, et al		Cardiovasc Intervent Radiol 2010;	12	Na	6	100	Na	Na	Na	Na
	Castle, et al		Urology 2011	10	Na	17.9	Na	62	Na	Na	Na
	Yu, et al		Radiology 2012	46	49	20.1	98		100	92.3(3yr)	97.8(3yr)
HIFU	Moreland, et al		J Endourol 2014	53	55	8	100***	100***	Na	Na	Na
	Ritchie, et al		BJU Int 2011	12	Na	15	58.3	100	Na	Na	Na
	Hacker, et al		BJU Int 2006.	19	19	Na	Na	Na	Na	Na	Na

* Biopsi proven RCC
**Available 17 patients
***Available 38 patients
Na: Not available

a median follow-up of 8 months none of 38 patients (0%) demonstrated evidence of local recurrence or metastasis. 98% of patients were able to discharge on the day following the operation [31].

High-İntensity Focused Ultrasound (HIFU)

High- intensity focused ultrasound (HIFU) technique uses physical effect of ultrasound (US) energy to cause coagulation necrosis on the tissue. A focused US beam leads to mechanical vibrations in the tissues, which produce heat. Rapidly increased heat results in protein denaturation thus cell destruction and coagulation necrosis with a threshold of 60° C. The efficacy of this thermal necrosis depends on several factors such ultrasound frequency, absorption coefficient, perfusion rate in the targeted tissue, acoustic reflection and refraction, exposure time and transducer characteristics. HIFU can be applied both extracorporeally and laparoscopically. HIFU is considered the most minimally invasive technique among the ablative treatments such there is no need of insertion of a probe into the tissue, which may result in hemorrhage and tumor spillage. Other possible advantages include decreased morbidity, reduced postoperative pain, shorter hospitalization, preservation of renal function, and no need of general anesthesia or skin incision [32, 33]. To avoid tissue attenuation and respiratory movement of the kidney, a laparoscopic approach can be preferred. By attaching a HIFU transducer to a laparoscopic probe; US energy can be apply directly to the renal tumor surface.

Briones et al. suggested HIFU as a promising but investigational method due to small number of treated patients and technologic incompetence in their review article [34]. In a study conducted with 12 patients, HIFU was found a safe and feasible technique for ablation of renal tumors with comparable oncologic efficacy with other options [35].

Hacker et al. reported the outcomes of 19 patients requiring RN for renal tumors who underwent extracorporeal HIFU prior to nephrectomy. They found no systemic adverse effects during or after the procedure. Two patients had a localized grade 3 skin burn. Pathologic examinations revealed no subcapsular or perirenal hematomas and no thermal injury to the ureter, renal pelvis or renal vascular pedicle. Various morphological signs of tissue ablation were noticed in 15 kidneys and there was no correlation with administered US energy [36].

Klingler et al. reported promising results from their phase I clinical study. They treated ten kidneys with solitary kidneys ranging from 12 mm to 90 mm. Laparoscopic nephrectomy was performed subsequent to HIFU in 2 patıents with 9 cm tumors. The remaining seven underwent laparoscopic partial nephrectomy and one was managed with post-HIFU biopsies and radiologic follow-up. Four of seven tumors extirpated after HIFU showed complete ablation of the whole tumor. Two had 1 to 3 mm viable tissue adjacent to HIFU targeted area and one tumor possessed vital tissue about 20% of its central area. They reported no intra or postoperative complications related to HIFU [37].

Discussion

The development of technology leads new techniques in the field of health. The refinement of laparoscopy and then the use of robot-assisted surgery have created great excitement in the management of renal masses. On the other hand, both patients and physicians have become more concerned with minimally invasive techniques along this time. Minimally invasive techniques offer a less debilitating treatment process even they can be performed on an outpatient base. Minimal invasive techniques can be a feasible treatment alternative for patients who have high surgical and anesthetic risk with multiple comorbidities, have multiple tumors due to a systemic disease like VHL or do not want to undergo extirpative surgery. Especially elderly patients can be good candidates for these procedures with their relatively short life expectance and impaired performance status.

As we discuss previously minimal invasive treatment of small renal masses consist of various ablative techniques such as RFA, CA, MWA and HIFU. The clinical studies on MWA and HIFU are less compared to RFA and CA. Thus MWA and HIFU remain still experimental due to low patient volume and insufficient clinical experience. The methodology of the studies in the literature varies which makes it difficult to make a comparison between these techniques.

In many clinical studies, it is postulated that minimal invasive techniques particularly RFA and CA have similar CCS, DFS, RFS and OS rates compared to nephrectomy. Besides their favorable oncologic outcomes, their complication profile is acceptable and even less compared to extirpative surgery. The preservation of renal function, shorter operative times, smaller estimated blood loss and easy application comprise other potential advantages. These techniques also present an improved patient procedural tolerance with a shorter hospital stay and more comfortable postoperative course. Using laparoscopic approach may improve technical success but it hampers the minimal invasive aspect of these techniques.

The follow-up procedures may require consecutive CT imaging. Physicians must be aware of the secondary neoplasms related to that radiation exposure. Thus, definitive follow-up schemes must be establish.

In conclusion, aforementioned techniques for the management of small renal masses are promising with their high efficacy and good short and intermediate term results. Controlled randomized trials with large patient volume and long-term follow-up are mandatory particularly for MWA and HIFU.

Competing interests

The authors declare that they have no competing interests

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