Original Article

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Radiofrequency ablation for adenoma in patients with primary aldosteronism and hypertension: ADERADHTA, a pilot study

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Objective: To evaluate the efficacy and the feasibility of radiofrequency ablation to treat aldosterone-producing adenomas.

Methods: In an open prospective bicentric pilot study, patients with hypertension on ambulatory blood pressure measurement, a primary aldosteronism, an adenoma measuring less than 4 cm, and confirmation of lateralization by adrenal venous sampling were recruited. The primary endpoint, based on ABPM performed at 6 months after the radiofrequency ablation, was a daytime SBP/DBP less than 135/85 mmHg without any antihypertensive drugs or a reduction of at least 20 mmHg for SBP or 10 mmHg for DBP.

Results: Thirty patients have been included (mean age = 51 ± 11 years; 50% women). Mean baseline daytime SBP and DBP were 144 ± 19/ 95 ± 15 mmHg and 80% received at least two antihypertensive drugs. At 6 months: 47% (95% CI 28–66) of patients reached the primary endpoint, mean daytime SBP and DBP were 131 ± 14 (101–154)/87 ± 10 (71–107) mmHg; 43% of them did not take any antihypertensive drug and 70% of them did not take potassium supplements. Few complications were recorded: four cases of back pain at day 1 postablation; three limited pneumothoraxes, which resolved spontaneously; one lesion of a polar renal artery.

Conclusion: Radiofrequency ablation for hypertensive patients with aldosterone-producing adenomas seems to be an emerging promising alternative to surgery. Its efficacy and its feasibility have to be confirmed in a larger sample of patients.

Keywords: adrenal adenoma, hypertension, primary aldosteronism, radiofrequency ablation

Abbreviations: ABPM, ambulatory blood pressure monitoring; AE, adverse events; APA, aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; AVS, adrenal venous sampling; BP, blood pressure; RFA, radiofrequency ablation

INTRODUCTION

Primary aldosteronism is characterized by hypertension, frequent hypokalemia, and an inappropriately high aldosterone-to-renin ratio (ARR) [1,2]. Aldosterone-producing adenoma (APA or Conn syndrome) is one of the main causes of primary aldosteronism [3]. Laparoscopic total-adrenalectomy is an option to normalize or at least improve blood pressure (BP) control, hypokalemia, and normalize the ARR [4,5].

However, the reported result of surgery is around 50% of clinical cure rate with an overall complication rate of 9.5% [2,6–8].

An efficient but less invasive alternative technique could be the use of radiofrequency ablation (RFA). RFA is widely used to treat solid neoplasms, especially in patients not only with primary or secondary malignancies of the liver, the lung, the kidney, and the breast but also for primary and metastatic adrenal neoplasms, including adrenocortical carcinomas [9–15]. More recently, RFA has been used for patients with primary aldosteronism and unilateral adenoma [16–25]. These studies focused on hormonal resolution of primary aldosteronism, computed tomography (CT) aspects, and safety data after RFA but the putative positive impact on BP control was not clearly depicted [16–25].

The aim of this study is, therefore, to assess whether RFA improves ambulatory BP control in patients with

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hypertension because of primary aldosteronism and unilateral adrenal adenoma. Normal potassium, ARR values and safety of the procedure are the secondary outcomes.

METHODS

Trial design

The trial was a national, prospective, multicentric, single-arm experimental pilot study.

Participants and inclusion criteria

Between November 2016 and October 2018, we enrolled patients from two French Hypertension Excellence Centers (Toulouse and Bordeaux) who were 18 years old or older, had hypertension confirmed with ambulatory blood pressure monitoring (ABPM), and primary aldosteronism demonstrated by hormonal assays and unilateral APA. After 35 years of age, all patients with primary aldosteronism underwent adrenal venous sampling (AVS) [4].

Blood pressure measurement and antihypertensive strategy

BP was measured by 24-h ABPM (Spacelab device Healthcare SAS, France in Toulouse and Diasys integra 2, Novacor, in Bordeaux, France). The cuff with an appropriate size was set up on the left arm by a training nurse at each hypertension excellence center.

Three or four ABPM were performed: at inclusion and at 1, 3 (optional), and 6 months after RFA.

Hypertension was defined as a daytime ABPM over 135/85 mmHg at inclusion.

After RFA, aldosterone antagonists were removed and not reintroduced until 6 months of follow-up. Antihypertensive treatment was adjusted according to the BP level measured during the follow-up to reach the target of a daytime ABPM below 135/85 mmHg.

Aldosterone-producing adenoma diagnosis

The diagnostic work-up of APA included the biochemical diagnosis of primary aldosteronism, evidence of adrenocortical adenoma on a CT scan, and/or unequivocal evidence of lateralized aldosterone secretion if adrenal venous sampling was available.

Hormonal part

Plasma aldosterone concentrations were measured by radioimmunoassay. Depending on the center, direct renin concentration was measured by chemiluminescent immunoassay or plasma renin activity was measured by radioimmunoassay. Samples were collected in the supine position or after 15 min in the sitting position. As recommended, a minimum renin value of 5 mIU/l was used to calculate the ARR [26]. All drugs interfering with the renin–aldosterone system were suspended approximately 2 weeks before evaluation (6 weeks for aldosterone antagonist). A cut-off value of the ARR of 23 (plasma aldosterone in pg/ml and direct renin in mIU/l) or 64 (plasma aldosterone in pmol/l and direct renin in mIU/l) was used as the reference. Primary aldosteronism was defined according to the 2016 French consensus by an ARR greater than 64 (or >23 according to the unit) repeated twice [26]. If aldosterone less than 550 pmol/l or less than 200 ng/l, a confirmatory testing in the form of a captopril infusion or salt-loading test was performed depending on center practice.

Adenoma and lateralization

First, a unilateral adenoma less than 4 cm and with a homogenous contrast less than 10 Hounsfield Unit (HU) or, if not, absolute contrast wash-out greater than 60% has to be diagnosed by radiologist based on CT imaging.

AVS was then performed after 35 years of age in each center without cosyntropin stimulation and in a sequential manner. Cannulation was successful when adrenal/peripheral venous cortisol gradients were greater than 2 and lateralization was assessed by comparison of right and left adrenal venous aldosterone/cortisol ratios with a cut off value greater than 4 ipsilateral to the nodule side to define a positive lateralization of secretion [27,28].

Exclusion criteria were patients with previous pneumothorax, coagulopathy syndrome, potentially inaccessible tumor without well tolerated puncture access according to the radiologist.

Ethics

Benefits and drawbacks of participating in the trial were explained to eligible patients and written informed consent was obtained from all patients. The work was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by an ethics committee and the French Competent Authorities.

Written information was given to patients, including conditions governing anonymity and study withdrawal. The trial is registered at ClinicalTrials.gov under the number NCT02756754.

Intervention: radiofrequency ablation procedure

The procedure was restricted to one or two interventional radiologists in each center, each of whom had experience in the performance of RFA on other organs, such as solid kidney nodular lesions. All RFA procedures were performed under general anesthesia to avoid pain and motion and to precisely target adrenal lesion [29]. Radial arterial pressure monitoring was used and pharmacologic adjustments were made, if necessary, to avoid hypertensive crisis, and postprocedure inpatient hemodynamic monitoring was also required [15]. Under real-time multidetector CT guidance, patients were treated in prone or decubitus position with regard to optimal RFA needle access route. In patients in whom the adrenal tumors were adjacent to an organ and prior to needle insertion, hydrodissection could be employed, if necessary, to protect the surrounding organs before radiofrequency energy was applied [30]. Two types of monopolar RFA needles were used: single needle electrodes (Soloist Single Needle Electrodes) or umbrella-shaped needle electrodes (LeVeen Needle Electrode Family), depending on the size of the tumor, and used with an RF 3000 generator (by Boston Scientific, Natick, Massachusetts, USA) [10]. Single needles electrodes were initially used for small tumors to prevent surrounding organ

damage, whereas umbrella-shaped needles were employed for larger ones. Thermal ablation was performed according to the manufacturer' instructions. A CT scan immediately assessed the extent of tumor ablation.

Follow-up

Patients were closely monitored the day following RFA and were discharged between 1 and 3 days later if no immediate complications occurred. Aldosterone antagonists were discontinued and other antihypertensive drugs or potassium supplements were titrated according to BP control and potassium levels before discharge. Patients visited the hospital, 1 month, 3 months (optional visit) and 6 months after RFA to assess the primary outcome. They underwent routine physical examination, antihypertensive drugs were recorded, and ABPM and hormonal tests were performed. CT scans were obtained 1 month after the procedure to assess necrosis of the tumor (lack of enhancement indicated complete treatment and residual enhancement meant residual disease).

Outcomes

Primary outcome

The primary composite outcome is defined as daytime SBP/DBP less than 135/85 mmHg at 6 months measured by ABPM without antihypertensive treatment or a decrease in daytime SBP of 20 mmHg or of DBP of 10 mmHg between baseline and 6 months [31].

Secondary outcomes were evaluation of potassium levels according to potassium supplementation, normalization of the ARR, and description of the CT scan appearance of the adrenal gland after RFA.

Safety

Among all the postoperative complications, prespecify data were also recorded, that is, retroperitoneal hematoma, pneumothorax, pain, and infection. Moreover, any adverse event that occurred during the 6-month follow-up period was checked.

A monitoring committee carried out a review of the safety and efficacy for the first 13 patients. Regarding efficacy, they observed a high proportion of failures among patients treated with a single needle electrode ($n = 5$) and a high proportion of improvement among patients treated with umbrella-shaped needles ($n = 8$). They recommended discontinuing single needle electrodes. The protocol was amended to follow this recommendation and was validated by the ethics committee.

Statistical analyses

Descriptive statistical analyses were carried out. The percentage of patients with normalized BP was estimated with a 95% confidence interval. For the primary outcome and secondary outcome components at 6 months, we considered missing values to be 'failures' for patients lost-to-follow-up before 6 months (worst-case scenario approach), and we applied the 'last observation carried forward' (LOCF) principle for the other missing values.

RESULTS

A total of 30 patients with APA were included. One patient treated by umbrella-shaped needle electrode was lost to follow-up after 1.1 months, and one patient treated by single needle electrode dropped out of the study at 5.1 months of follow-up. Despite premature discontinuation, those two patients who still had hypertension or primary aldosteronism at the last follow-up were included in the final analysis and considered as failure.

Baseline characteristics

These are summarized in Table 1. The mean age of patients was 51 ± 11 years (range: 32–75 years), 50% were women, and the mean duration of hypertension was 12 ± 10 years. At baseline, mean daytime SBP/DBP was 144 ± 19 (range 116–190)/95 ± 15 (range 75–130) mmHg. Eighty percent of patients were treated with at least two antihypertensive drugs. Ninety percent received aldosterone antagonists just before RFA (median daily dose of 52.5 mg (range 12.5–250 mg) (Supplemental digital content 1, http://links.lww.com/HJH/B505). AVS was performed in all patients but one aged 32 years.

Primary outcome

At 6 months, the primary outcome was reached for 47% [95% confidence interval (CI) 28–66] of patients. Mean daytime BP was 131 ± 14 (101–154) / 87 ± 10 (71–107) mmHg; 12 patients ($12/28 = 43\%$) received no antihypertensive treatment of which seven ($7/28 = 25\%$) had normal daytime BP. Fifty-two percent (95% CI 31–72) of patients reached the primary outcome when RFA was performed with umbrella-shaped needles (Table 2).

Secondary outcomes

The serum potassium level was normalized without potassium supplementation, aldosterone antagonist, or amiloride in 70% (95% CI 51–85) of all the patients, and in 84% (95% CI 64–96) of patients treated with umbrella-shaped needles.

Hormonal success (normalization of the ARR) was obtained at 6 months in 77% (95% CI 58–90) of all the patients, and in 92% (95% CI 74–99) of patients treated by umbrella-shaped needle (Table 2).

Tumor size at inclusion was 14.9 ± 5.4 mm, and 67% of the tumors were located in the left gland. Lesions remained hypodense without contrast enhancement at 1 month after RFA in 23 out of 28 patients (82%, 95% CI 63–94), and five patients had unchanged density (all of them without clinical success) (Supplemental digital content 2, http://links.lww.com/HJH/B505).

No association between the side of the tumor and clinical success was recorded (45% success for the left side and 50% success on the right side).

Both daytime and night-time BP improved significantly and the total number of antihypertensive agents decreased after RFA (Supplemental digital content 2, http://links.lww.com/HJH/B505).

Safety

Eleven patients (36.7%, 95% CI 19.9–56.1) experienced 14 RFA-related adverse events (causality assessed by

TABLE 1. Baseline characteristics at inclusion

	Needle type		
	Umbrella-shaped ($N=25$)	Single needle ($N=5$)	Total ($N=30$)
Age (years), mean ± SD	50.0 ± 11.0	55.8 ± 10.9	50.9 ± 11.0
Duration of hypertension (years), mean ± SD	11.9 ± 10.5	9.6 ± 6.6	11.5 ± 9.9
Baseline daytime ABPM SBP (mmHg), mean ± SD	143.8 ± 20.0	144.4 ± 8.9	143.9 ± 18.5
Baseline daytime ABPM DBP (mmHg), mean ± SD	95.2 ± 16.1	96.2 ± 4.4	95.4 ± 14.8
Sex [*n* (%)]			
Male	12 (48.0%)	3 (60.0%)	15 (50.0%)
Center [*n* (%)]			
Toulouse	11 (44.0%)	1 (20.0%)	12 (40.0%)
Bordeaux	14 (56.0%)	4 (80.0%)	18 (60.0%)
Smoking [*n* (%)]	6 (24.0%)	3 (60.0%)	9 (30.0%)
Family hypertension [*n* (%)]	17 (68.0%)	1 (20.0%)	18 (60.0%)
Body mass index (kg/m^2), mean ± SD	27.1 ± 5.0	25.5 ± 2.6	26.9 ± 4.7
Hypokalemia[*n* (%)]	24 (96.0%)	4 (80.0%)	28 (93.3%)
Potassium* (mmol/l), mean ± SD	3.7 ± 0.6	3.6 ± 0.4	3.7 ± 0.5
Glomerular filtration rate* (ml/min, MDRD formula), mean ± SD	90.8 ± 29.1	100 ± 10.9	92.4 ± 26.9
CT scan, tumor on the left side [*n* (%)]	18 (72.0%)	2 (40.0%)	20 (66.7%)
CT scan, tumor average diameter (mm)*, mean ± SD	14.6 ± 5.7	16.4 ± 3.0	14.9 ± 5.4
Total antihypertensive defined daily dose (DDD), mean ± SD	2.7 ± 1.7	1.8 ± 1.3	2.5 ± 1.7
Number of antihypertensive agents, mean ± SD	2.5 ± 1.2	2.4 ± 1.1	2.5 ± 1.2
Detailed number of antihypertensive agents [*n* (%)]			
1	5 (20.0%)	1 (20.0%)	6 (20.0%)
2	10 (40.0%)	2 (40.0%)	12 (40.0%)
3	5 (20.0%)	1 (20.0%)	6 (20.0%)
4–6	5 (20.0%)	1 (20.0%)	6 (20.0%)
Patients with potassium supplementation [*n* (%)]	10 (40.0%)	2 (40.0%)	12 (40.0%)
Potassium supplementation DDD, mean ± SD	0.5 ± 0.8	0.7 ± 1.0	0.5 ± 0.8
Spironolactone at inclusion [*n* (%)]	13 (52.0%)	4 (80.0%)	17 (56.7%)
Spironolactone (mg) at inclusion, mean ± SD	57.7 ± 57.4	37.5 ± 14.4	52.9 ± 50.9
Pathological aldosterone-to-renin ratio [*n* (%)]	25 (100%)	5 (100%)	30 (100%)

ABPM, ambulatory blood pressure monitoring; CT, computed tomography; MDRD, Modification of Diet in Renal Disease; SD, standard deviation.

investigator as 'possible' or 'doubtful') (Table 3). Among them, three small pneumothoraxes (<3 mm) that resolved spontaneously without requirement of a drainage procedure and four cases of transient postoperative pain managed with acetaminophen tablets were recorded.

Two serious RFA-related adverse events were reported, that is, requiring a hospitalization or its prolongation: one patient experienced per procedural polar renal artery damage and recovered without renal sequelae. The other patient complained of chest pain after the RFA, has a diaphragm lesion depicted on the CT scan, received antalgic drugs, and was discharged from the hospital 2 days later (Supplemental digital content 3, http://links.lww.com/HJH/B505: detailed description of these two cases).

No adverse event led to RFA procedure discontinuation. RFA-related adverse events were not associated with the side of the tumor.

DISCUSSION

In our study, RFA performed in patients with hypertension, primary aldosteronism, and unilateral adrenal adenoma led to normalization or improvement of their BP in 47% (14/30) of them after a 6-month follow-up period. Potassium was in

TABLE 2. Outcomes at 6 months, observed values ($n=28$) and after imputations for missing values ($n=30$)

	Needle type		
	Umbrella-shaped ($N=25$)	Single needle ($N=5$)	Total ($N=30$)
Primary outcome			
n success[b]/*N* total (%) [95% CI]	13/24 (54.2%) [32.8–74.4%]	1/4 (25.0%) [0.6–80.6%]	14/28 (50.0%) [30.6–69.4%]
n success[b]/*N* total[a] (%) [95% CI]	13/25 (52.0%) [31.3–72.2%]	1/5 (20.0%) [0.5–71.6%]	14/30 (46.7%) [28.3–65.7%]
Secondary outcomes			
Potassium ≥3.6 mmol/l without potassium supplementation, *n* (%) [95% CI]	18/21 (85.7%) [63.7–97.0%]	0/2 (0%) [0–84.2%]	18/23 (78.3%) [56.3–92.5%]
Potassium ≥3.6 mmol/l without potassium supplementation[a], *n* (%) [95% CI]	21/25 (84.0%) [63.9–95.5%]	0/5 (0%) [0–52.2%]	21/30 (70.0%) [50.6–85.3%]
Normalized aldosterone-to-renin ratio, *n* (%) [95% CI]	19/19 (100%) [82.4–100%]	0/2 (0%) [0–84.2%]	19/21 (90.5%) [69.6–98.8%]
Normalized aldosterone-to-renin ratio[a], *n* (%) [95% CI]	23/25 (92.0%) [74.0–99.0%]	0/5 (0%) [0–52.2%]	23/30 (76.7%) [57.7–90.1%]

CI, confidence interval.
[a]After imputation of missing outcomes.
[b]Successes are defined as daytime SBP/DBP less than 135/85 mmHg at 6 months measured by ABPM without antihypertensive treatment or a decrease in daytime SBP of 20 mmHg or of DBP of 10 mmHg between baseline and 6 months.

TABLE 3. Summary of safety results

	Needle type		
	Umbrella-shaped	Single needle	Total
	$N=25$	$N=5$	$N=30$
Patients with at least one AE [*n* (%)]	18 (72%)	2 (40%)	20 (66.7%)
Patients with at least one serious AE [*n* (%)]	5 (20%)	0 (0%)	5 (16.7%)
Patients with at least one RFA-related AE [*n* (%)]	11 (44%)	0 (0%)	11 (36.7%)
Patients with at least one serious RFA-related AE [*n* (%)]	2 (8%)	0 (0%)	2 (7%)
Safety-specific secondary outcomes			
Pneumothorax	3	0	3
Transient post-RFA pain	3	0	3
Retroperitoneal hematoma	0	0	1
Infection	0	0	1
Number of RFA-related AEs ($n=14$)[a]			
Pneumothorax	3	0	3
Transient post-RFA pain	3	0	3
Dorsalgia	1	0	1
Renal polar arterial injury	1	0	1
Chest pain[c]	1	0	1
Malaise	1	0	1
Small adjacent hepatic RF injury	1	0	1
Chronic kidney failure[b]	1	0	1
Acute kidney failure[b]	1	0	1
Vomiting	1	0	1

RFA, radiofrequency ablation.
[a]Fourteen (14) RFA-related adverse events (AE)s in 11 patients.
[b]Acute and chronic kidney failure were declared for the same patient.
[c]Chest pain was a 'serious' event leading to the prolongation of hospitalization.

the normal range in 70% of the cases and primary aldosteronism was cured in 77% of patients.

Data and clinical success after radiofrequency ablation

To our knowledge, this is the first trial that focuses on BP control as a primary outcome defined using ABPM.

Previous series of RFA for APA treatment have been already published in which BP improvement varied widely from 17 to 67%. All but one retrospective comparison between RFA and adrenalectomy suggested no differences in BP control [21,23,24,32]. Liu *et al.* [32] reported that hypertension was less frequently cured after RFA than after surgery (36 vs. 70%; $P=0.007$). To improve BP control, repeat RFA sessions may be needed in a number of patients. Other short series of one to nine patients were also reported, not allowing to draw conclusions about BP control [16,17,22,25,33].

Several factors contribute to explain the discrepancy between our results and those reported in other studies (Supplemental digital content 4, http://links.lww.com/HJH/B505). The main one is that we used ABPM, which is the gold standard to measure BP in a much more robust manner than casual measurements reported elsewhere [18,20,21,23,24,32].

In our study, the choice of the type of needle electrode played a critical role for the success of the RFA, and umbrella-shaped needle electrodes should certainly be preferred to single needle ones. Radiologists used single needle electrodes in case of small adrenal tumors to prevent adjacent organ damage but they failed to improve BP in our experience with 100% failure (5/5). Umbrella-shaped needle electrodes ensured adequate destruction of the tumor tissue, increased the rate of clinical success, and should be selected whenever possible. Nevertheless, a review pointed out that not all patients with APA are candidates for RFA, and this constituted a limitation of the technique [34].

Data and clinical success regarding surgery

In the absence of a randomized clinical trial, which compared RFA to surgery in this indication, it is certainly impossible to draw definite conclusions. Supplemental digital content 5, http://links.lww.com/HJH/B505 provides some elements in terms of BP change from baseline. Applying the PASO study criteria, we report 67% (95% CI 47–83) of complete or partial clinical success. When hormonal data are taken into consideration, primary aldosteronism was resolved in 77% of patients (23 of 30) after RFA. However, these clinical and hormonal success remain lower than those obtain with surgery in this study (>90% for both) [2]. In a recent French multicentric prospective trial, 30.4% of patients at 6 months were cured by surgery (24 h ABPM <130/80 mmHg) [35]; with the same BP criteria after RFA, the success rate was about 35% (Supplemental digital content 2, http://links.lww.com/HJH/B505).Thus, in a French sample of patients, the efficacy of the surgery seemed to be close to what was obtained with RFA.

The clinical success reported after surgery of APA varied widely according to the patient characteristics [36]. Variations are attributed to age, sex ratio, duration of hypertension, and other underlying factors [2]. In our study, none of these factors including, sex, age, duration of hypertension, number of antihypertensive drugs, BP at baseline, and renal function seemed to be significantly associated with BP improvement (Supplemental digital content 6, http://links.lww.com/HJH/B505).

However, important points must be underlined: unilateral laparoscopic adrenalectomy has now been performed for many years. RFA is a new method, which requires a learning curve. The choice of adequate material is also important as demonstrated in this report. The results we obtained do not seem to be very different from the surgical results and in our opinion should probably improve. Two important issues may, in the future, rule in favour of this new method: a potential reduction in cost, which has to be confirmed in a trial and the fact that RFA has a more selective effect compared with the usual surgical procedure involving a complete removal of the gland.

Safety

Considering that 36.7% of patients experienced RFA-related adverse events, and only two serious ones, CT-guided percutaneous RFA seems relatively well tolerated and comparable with other studies [20,28,37]. Although previous series have shown postprocedural hematoma or infection, none occurred in our study [11,20].

This study has several limitations: first, it is a pilot prospective study without a control group. Therefore, we do not compare the RFA to surgery. However, our data suggest a significant improvement in terms of BP control and hormonal status through a less invasive management than the standard surgery. Second, we used two different electrodes: single needle electrodes and umbrella-shaped needle electrodes. The limit of the single needle electrode was not previously reported in this indication. The use of this needle in five patients impairs the global results of our study. When we focus on patients treated with the umbrella-shaped needle, 92% of the patients normalized their ARR. Third, the follow-up period was short (6 months). However, no long-term recurrence rate was reported in a previous study [20]. Fourth, these results are preliminary, particularly concerning the safety of the procedure, and this should be further evaluated, in a larger population.

In conclusion, RFA seems to be a reasonable alternative to surgery in hypertension related to APA. The next step is to perform a large prospective randomized trial comparing RFA to surgery with long-term outcome assessment. Although superiority of one method over the other is uncertain in terms of BP control and biochemical cure, differences could be expected in terms of side effects and costs.

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Conflicts of interest

There are no conflicts of interest.

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