



# Outcomes following minimally invasive image-guided percutaneous ablation of adrenal glands

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**Abstract:** Whilst surgery represents the gold standard for the treatment of adrenal primary malignant tumors, metastatic involvement of the adrenal glands is generally approached conservatively; however, surgery for local control has been controversial, and several reports have described the utility of surgical removal in terms of prolonged survival in selected patients. Different techniques, including radiofrequency ablation (RFA), microwave ablation (MWA), laser induced thermal therapy (LITT), cryoablation (CRA), and chemical ablation, are employed in percutaneous image-guided ablation for primary and metastatic malignancies of the adrenal glands, in case of patients with multiple comorbidities or who refuse surgery. Technical success, clinical success and safety were analysed and discussed in this systematic review. Tumor size was found a significant determinant for local disease control; histology of the primary malignancy and coexistence of tumor elsewhere were correlated with prognosis. These procedures resulted to be feasible and safe, with hypertensive crisis representing the most common complication. Although there is lack of evidence in the literature concerning outcomes compared with surgery, percutaneous ablation may represent a useful therapeutic option for controlling unresectable adrenal metastases, offering patients opportunities for improved survival.

**Keywords:** Ablation techniques; adrenal glands; adrenal gland neoplasms; radiofrequency ablation; microwave ablation; laser-induced interstitial thermotherapy; cryoablation; chemical ablation

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## Introduction

Clinically unapparent adrenal neoplasms are frequently encountered in routine practice, found in 2–10% of the population worldwide (1), and the opportunity to discover adrenal masses is constantly increasing thanks to improved sensitivity of imaging techniques (2). Among adrenal lesions, malignancies are overall rare; however, the adrenal glands are a common site for metastases, particularly from lung cancer, renal cell carcinoma (RCC), colorectal cancer, hepatocellular carcinoma (HCC), and malignant melanoma, with adrenal metastases occurring in 3–27% of cancer patients as reported by autopsy reviews (3).

Metastatic involvement of the adrenal glands is generally treated conservatively, depending on the primary malignancy, by chemotherapy or radiation therapy; however, surgery for local control has been controversial, and several reports have described the utility of open surgical or laparoscopic resection in terms of prolonged survival in selected patients with isolated metastatic disease to the adrenal glands (4,5). Nonetheless, few patients are usually eligible for surgery because of multiple comorbidities, elder age, difficult approach due to altered anatomical planes and fibrosis for previous surgery, or concomitant extra-adrenal cancer.

In recent years, the drive behind the general trend toward minimally invasive procedures represents the result of a diverse combination of factors, primarily the obvious drawbacks of almost any surgical intervention, the development and refinement of new technologies, the aim to reduce peri-operative complications and post-operative recovery time especially in subjects debilitated or who refuse surgery, and patient awareness of emerging therapeutic approaches. Image-guided ablation techniques, successfully employed in diverse clinical scenarios, have been used also for the treatment of malignant adrenal masses. The purpose of this article was to analyse the current evidence on image-guided ablative procedures for malignant adrenal neoplasms in terms of safety and outcomes.

## Materials and methods/search strategy

An extended systematic search in Medline database (via PubMed), including articles related to human medicine was performed. Keywords were chosen according to Medical Subject Heading (MeSH) terms: “adrenal glands”, “adrenal gland neoplasms”, “ablation techniques”, used in combination with the Boolean operators OR and AND

respectively.

The bibliographic search provided a total number of 164 citations; two independent reviewers (A.C. and F.P.) screened the initial search results considering titles and abstracts. Both reviewers had experience in data extraction for retrospective and prospective studies. Articles addressing an issue pertinent to ablation of adrenal gland malignant lesions and reporting outcome data were considered potentially eligible for inclusion. In more detail, inclusion criteria were as follows: English-written, human studies dealing with ablation techniques [namely radiofrequency ablation (RFA), microwave ablation (MWA), laser-induced interstitial thermotherapy (LITT), cryoablation (CRA), chemical ablation] used for adrenal gland primary malignancies or metastases, with consideration of outcomes of the procedures; case series of more than 3 patients. Reviews, case reports and studies which did not perform outcome analysis were excluded. All the articles selected by at least one of the reviewers were retrieved for full text evaluation and were jointly discussed to obtain an agreement in case of uncertainty. Additional searches of their reference lists were performed to identify other potentially eligible articles. Data were consequently extracted using an extraction form designed for the purpose. Finally, 20 articles were considered relevant for the aims of the literature review and were therefore included in this work (*Table S1*).

When indicated, technical and clinical successes, disease free-survival and overall survival were reported. Moreover, also complications were reported. These outcomes were defined as follows:

### *Technical success*

The definition of technical success varies among different studies. In most studies, technical success rate, was defined as the completion of adrenal ablation according to the planned treatment protocol (6).

### *Clinical success*

Complete ablation was generally defined as no evidence of enhancing tissue in the treated adrenal gland at post-procedural imaging or at the first follow-up, and this means successful local control of disease; the visualization of any focal area of enhancement in the ablated lesion should be deemed as residual viable tumor at imaging evaluation performed 1 month after the procedure (7).

Local disease progression or recurrence was generally identified as the appearance at follow-up imaging (more frequently CT performed after 3 months from the procedure) of new enhancing nodules at the site of a previously treated lesion (7).

### ***Progression-free survival***

Progression-free survival was defined as the length of time after treatment during which a patient survives with no sign of the disease (3,7).

### ***Overall survival***

Overall survival was defined as the length of the time after treatment and the death of the patient from any cause (7).

### ***Safety***

All complications were recorded and classified as minor and major; they were assessed according to CTCAE (8). Major complications were defined as complications that, if left untreated, might threaten the patient's life, lead to substantial morbidity and disability, result in hospital admission or substantially lengthen hospital stay, as described by the International Working Group of Image Guided Tumour Ablation (7). Minor complications included typical post-ablation syndrome symptoms (fever, pain, nausea and vomiting) if present >4 days after the ablation procedure.

Complications were further divided into two causal categories: those secondary to device placement (pneumothorax, infection and bleeding) and in cases of thermal ablation, those secondary to thermal injury (damage to adjacent organs) (9). Hypertensive crisis (HC) is related to parenchyma destruction (10). HC has been defined as an increase of systolic blood pressure greater than 180 mmHg or an increase in diastolic pressure greater than 120 mmHg (10).

## **Results**

### ***Radiofrequency ablation (RFA)***

Technical success, when reported, is high, ranging from 93% to 100%.

In two cases (11,12) the procedure was terminated before complete ablation because the patients developed

HC during the manoeuvre, requiring adequate medical treatment; in one case (12) the ablation was suspended due to frequent ventricular fibrillation and consequent transient myocardial ischemia.

The response rate in terms of complete/partial ablation after the first session varies among the collected series, ranging from 77.3% to 100%; most residual tumors underwent repeated ablation sessions (2,3,6,12,13). Among different series collected, recurrence rate reported was up to 25% (3).

Major complications occurred in 0 to 12% of patients in different studies with inhomogeneous cohorts; these encompasses HC with myocardial ischemia (3,13,14), post-ablation syndrome, deep vein thrombosis leading to subsequent haemorrhage and splenectomy (15), acute renal failure, haemorrhage, heart failure, stroke (2), haemobilia and acute cholecystitis (3), massive pneumothorax (14), and arrhythmia (12). HC has a frequency up to 57% (3).

Overall survival rate at 3-year, when reported, ranges between 34% and 53%, with a mean follow-up of 26.3 to 37 months.

### ***Microwave ablation (MWA)***

Technical success is not reported.

MWA exerts a high local control rate with complete ablation after the first treatment session which varies between the collected series from 80% to 100%; partially ablated nodules were successfully retreated to total response with further ablative sessions in all cases (3,15-19).

Local recurrence rates are below 25% (3,16,20).

Botsa *et al.* (16) have found rates of local recurrence at 3-month and 1-year follow-up of 19.4%. In their study, lesions treated successfully with a single ablation were smaller than 3 cm in size, while patients who needed an additional session had a tumor diameter larger than 3 cm (16). Similar results have been found by Men and colleagues (20), reporting local recurrence rate for smaller tumors (i.e., with diameter  $\leq 3.5$  cm) significantly lower than that for greater lesions.

No major complications were reported by two out of three series describing MWA for adrenal tumors (17,19). HC was registered with a rate of 5.6 % (2/31) (20). Other frequent reported minor complications are pain, post-ablation syndrome, and mild hypertension (17,19).

Survival data are limited; studies dealing with the treatment of adrenal gland metastases from lung cancer report median overall survival time of 14.6 months and

12 months (16,20). During the follow-up, patients died due to the general progression of the tumor.

### **Laser-induced interstitial thermotherapy (LITT)**

Technical success is not reported.

Vogl *et al.* (21) have reported the use of CT-guided and MR-thermometry-controlled LITT in a small series of 9 patients presenting single adrenal gland nodules. Complete ablation was achieved in a single session for each tumor, producing a volume of necrosis with a mean diameter of 4.5 cm. After a mean follow-up of 10 months, 2 (22%) tumors demonstrated recurrence at the treated site; two patients died during the follow-up duration for systemic tumor progression.

There were no procedure-related complications.

### **Cryoablation (CRA)**

Technical success is not reported.

The response rate in terms of complete/partial ablation after the first ablation is high (90.3% to 92%); moreover, patients with residual disease were all successfully retreated in subsequent CRA sessions.

No major complications were reported in the 2 series analysed (22,23). Welch *et al.* (24) reported HC in 46% of the cases. Other minor complications included pleural effusion and back pain.

Overall survival rate is reported only by Welch *et al.* (24). One-, 3-, and 5-year survival rates were 83.9%, 45.0%, and 30.0% respectively; the presence of concomitant extra-adrenal disease was a poor prognostic factor, whereas they could not find any association between primary tumor histology and survival.

### **Chemical ablation**

Technical success is not reported.

Xiao *et al.* (25) treated 20 metastases in 14 patients. Percutaneous ablation was repeated an average of three times for small lesions and five for larger ones. The complete response rate was 30% at 24-month follow-up, whereas a partial response to treatment was verified in the remaining 70% of cases.

In the treatment of malignant lesions, Shibata and colleagues (26) ablated 9 metastases from HCC in 7 patients with two to four sessions per lesion. Post-procedural CT showed residual enhancing tissue in two lesions (22%),

which were bilateral metastases in the same patient. During the follow-up (6–36 months), 3 nodules (33%) were further increased in size, while the remaining were not; after 6–28 months, one patient died from liver failure, and two from extra-adrenal metastatic spread.

No major complications were registered in the 2 reported studies. Fever and pain were the most common adverse events, and one patient experienced adrenal insufficiency (25,26).

About 35.7% of patients died at 2 years due to extra-adrenal disease progression in the series reported by Xiao *et al.* (25).

## **Discussion**

Surgical resection, whenever possible, represents the gold standard for primary adrenal neoplasm treatment; conversely, surgery for local control in patients with adrenal metastases is still controversial in the literature. In patients who are poor surgical candidates or who refuse surgery, percutaneous image-guided ablation may be considered a valid alternative.

The best treatment strategy must be decided by a multidisciplinary team including the interventional radiologist, oncologist, surgeon, and endocrinologist (27,28), considering risks and benefits for patients with several comorbidities.

Besides the concerns of patient selection, tumor size represents a relevant factor to be considered while attempting to achieve complete tumor ablation: it seems clear that the smaller is the maximum diameter, the greater the likelihood of a successful complete ablation. Although a consensus has not been achieved yet on a threshold size, better results have been reported for adrenal masses smaller than 5 cm (3,29,30). Other investigators reported a lower threshold, i.e., 4 (22) or even 3 cm for lesions successfully treated with a single ablative session (11,16), or to prevent local tumor progression (2).

General contraindications to adrenal ablative therapy are similar to the contraindications of the same procedures applied to other organs. For instance, as with any image-guided procedure, the risk of haemorrhage must be taken into account; therefore coagulopathies should be corrected before the ablation, and the international normalized ratio (INR) should be less than 1.5 and platelet count greater than 50,000/ $\mu$ L (27).

In addition to careful access planning based on imaging assessment, some investigators have reported

that preprocedural or periprocedural adrenergic blockade may need to be implemented with the aim to prevent HC (13,15) in cases of nonfunctional tumors due to the sudden release into the systemic circulation of catecholamines normally stored in the adrenal medulla surrounding the tumor (23), and in cases of functional tumors this indication reflects guidelines on pheochromocytomas in the surgical literature (31). Fintelmann and colleagues (23) reported in their series a lower likelihood of HC in tumors greater than 4.5 cm with no visible viable gland; hence, preprocedural imaging may be also useful to estimate the risk of the most serious and relatively common side effect of otherwise well-tolerated procedures.

On the other hand, some reports have suggested that  $\alpha$ -blockade may not be routinely needed, as most of the HCs encountered were well-controlled after adequate medical treatment (11).

RFA is the most used ablative technique described in literature for the percutaneous treatment of adrenal lesions. Most articles collected for the literature review deal with RFA of adrenal metastases from RCC, lung carcinoma, HCC, melanoma, gastrointestinal tumors and other malignancies; however, RFA has been used to treat not only metastatic tumors but also primary and metastatic adrenocortical carcinomas (ACC) (30).

Mayo-Smith *et al.* (29) have described the use of RFA in adrenal gland metastasis treatment. They found that the average size of the two adrenal masses that demonstrated viable residual tumor after ablation was 6.0 cm, compared with 3.6 cm for completely ablated lesions, but this difference was not significant.

In fact, the size of the lesion to be treated is a significant predictor of residual disease after ablation. Recently, Zhou *et al.* (14) found that patients with residual tumor had significantly larger nodules, and identified the threshold of 3 cm to predict the likelihood of incomplete ablation. This finding may be explained by the local effect of RFA in tumor thermal damage, since only lesions limited in size [i.e., with a diameter smaller than 4 cm (6)] can be ablated with each application depending on the electrode type.

Accordingly, Hasegawa *et al.* (2) confirmed the threshold of 3 cm to be a significant factor affecting local tumor progression.

Comparing transarterial embolization (TACE) alone with a combination treatment of TACE with simultaneous RFA, Yuan *et al.* (32) concluded that the second strategy led to a better local control of adrenal metastases from HCC (75.0% of patients) compared with TACE alone (35.3%) at

the last follow-up assessment.

Really few data are available about the role of CRA; the results described outlined similar effectiveness to other thermal techniques employed for the same purpose, and local control rate (80.6%) was comparable to that of surgery (77–83%) (23).

Chemical ablation was considered a poor alternative in bilateral and large metastases (>5 cm in diameter), in which thermal ablation techniques may produce better results in terms of disease local control (32).

Few studies have analysed the benefits in terms of survival of adrenal ablation, because of small and inhomogeneous patient cohorts, different techniques applied, and short-term follow-up; moreover, it should be borne in mind that the eventual prognosis of patients strongly depends on the primary malignancy. This makes it difficult to compare the results from different series featuring adrenal ablation.

Frenk *et al.* (3), describing use of RFA, CRA and MWA to treat 46 adrenal metastases, indicated a median overall survival of 30 months, which was significantly worse in patients with non-small cells lung cancer (NSCLC), which was found a significant predictor of worse outcome. In the whole population, local control and overall survival at 2 years compared favourably with results of surgical removal based on a systematic review of the literature (33).

Age of 65 years or older and the presence of extra-adrenal tumors were also identified to be worse prognostic factors (2) in patients with adrenal metastases. Whether the first prognostic determinant is obvious, the latter may be explicated thanks to the higher disease stage even after RF ablation in subjects presenting concomitant extra-adrenal disease.

Another retrospective study (16) included 71 patients with single adrenal metastases from NSCLC, treated by RFA (n=35) or MWA (n=36); the investigators revealed a median overall survival time of 14.0 months, with no significant difference in survival between the two different technique groups.

The aforementioned work by Yuan and colleagues (32) suggested that a combined therapy for adrenal metastases from HCC may be more effective than TACE alone: the overall survival rate was significantly higher in the group of patients receiving TACE+RFA therapy than in the TACE alone group (at 3 years 55.3% *vs.* 44.0%), in spite of more complications related to RFA usage that were shown to easily resolve after active management.

Percutaneous image-guided techniques are safe and well-tolerated procedure; HC is the most frequent complication

reported. However, most cases were successfully treated by prompt medical intervention, and ablations were successfully completed (6). The risk of sudden blood pressure increase is greater during treatment of tumors adjacent to viable adrenal parenchyma than during ablation of larger tumors localized in a gland completely occupied by the lesion (23).

There is disagreement about the role of MWA in inducing HC: some authors have suggested that the rapid rise in temperature may produce such complication more frequently than RFA, due to an excessive release of catecholamines; conversely, other investigators have reported that the risk with MWA could be lower, due to the shorter application time (18,19,24).

Welch *et al.* (24) and Zhang *et al.* (34) performed a hemodynamic change analysis during percutaneous adrenal CRA, and concluded that these patients should be pharmacologically pre-treated in a way similar to patients undergoing surgery for pheochromocytoma.

Others minor complications more frequently encountered included pain, post-RFA syndrome, minimal pneumothorax, transient urinary retention or bleeding, reduced renal function, retroperitoneal abscess, small haematoma, and transient arrhythmia, as shown in *Table S1*.

## Conclusions

Percutaneous image-guided ablation for primary and metastatic malignancies of the adrenal glands is feasible and safe, with zero mortality and negligible morbidity. Currently, there are no large randomized controlled trials which demonstrate the efficacy of this treatment strategy in terms of local progression and survival, compared with surgical removal. However, percutaneous ablation is a useful therapeutic option for controlling unresectable adrenal metastases, offering patients opportunities for improved survival.

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Table S1 Outcomes of patients who underwent percutaneous ablation for malignant adrenal tumors in the studies collected

Author, year	Tumor no.	Patient no.	Ablation technique	Age (years)	Tumor histology	Mean tumor size (mm)	Mean follow-up (months)	Technical success	Response rate (complete/partial ablation)	Recurrence rate	Complications	Survival
Wood 2003 (30)	15	8	RFA	NA	ACC recurrences or metastases	43 [15–90]	10.3 [1–20]	NA	Complete ablation	Recurrent disease 20% (3/15)	No periprocedural complications, 1 delayed multimicrobial abscess in a 90-mm after his third RFA	NA
Mayo-Smith 2004 (29)	11	10	RFA	58 [40–77]	Metastases from lung (n=5), RCC (n=4), melanoma (n=2)	39 [10–80]	11.2 [1–46]	NA	Partial ablation 18.2% (2/11)	No recurrence	No major complications Adrenal insufficiency (n=1), small hematoma (n=1)	6/10 patients (60%) died at 3–16 months for metastatic spread
Carratiello 2008 (6)	6	6	RFA	67.2 [55–74]	Metastases from RCC (n=3), breast (n=1), lung (n=1), ovarian cancer (n=1)	29 [15–40]	21 [6–36]	100%	Partial ablation 16.7% (1/6); complete ablation of the lesion after second RFA session (10 days)	No recurrence	No major complications; severe hypertension (n=1); post-RFA syndrome (n=1)	NA
Mouracade 2009 (22)	5	5	RFA	69.4 [57–87]	Metastases from RCC (n=5)	39 [20–60]	12	NA	NA	Recurrent disease 20% (1/5) at 1 year	No periprocedural complications abscess of the adrenal gland (n=1)	NA
Wolf 2012 (13)	20	19	RFA [16]	61 [40–84]	Metastases from RCC (n=7), lung (n=6), melanoma (n=2), endometrial carcinoma (n=1)	42 [20–80]	14 [1–67]	100%	Partial ablation 18.7% (3/16); 2 metastases from RCC in the same patient, then retreated; 18-cm melanoma metastasis)	NA	1 major complication (HC with myocardial ischemia); hypertensive crisis (n=1); hematoma (n=1)	Progression of primary disease at extra-adrenal sites leading to death (16/19 patients; 84.2%), 3/19 remain alive at 6.3 years, 4.4 years, and 2.6 years post ablation
			MWA [4]		Metastases from lung (n=2), small bowel malignancy (n=1), HCC (n=1)		14.5 [3–28]		Complete ablation			
Welch 2014 (15)	37	32	RFA [10]	66 [44–88]	Metastases from RCC (n=16); melanoma (n=7); colorectal cancer (n=4); other malignancies	18 [8–28]	26.6	NA	Partial ablation 2.8% (1/36)	Local recurrence 8.8% (3/34); post CRA n=2, post RFA n=1	8.6% rate of major complications: post-ablation syndrome (n=2); deep vein thrombosis and splenectomy (n=1)	Overall survival at 36 months 52%, with a median survival of 34.5 months
			CRA [27]			32 [12–80]				Recurrence-free survival at 36 months 88%	45.7% rate of hypertensive crises	
Hasegawa 2015 (2)	41	35	RFA, RFA + AE in 12 patient [34%]	64.7±9.6	Metastases from: NSCLC (n=15), RCC (n=9), colorectal cancer (n=5), HCC (n=4), and breast cancer (n=1), thymic cancer (n=1)	33 [12–82]	30.1 [1.2–96.8]	100%	Partial ablation 17% (6/35); after retreatment 6% (2/35)	Local tumor progression 8/35 patients (23%); primary local tumor progression rates 29.5% at 1 year and 43.6% at 3 and 5 years	8.3% (4/48) of major complication: acute renal failure, hemorrhage, heart failure and stroke 44% (21/48) of minor complications	1-, 3-, and 5-year overall survival rates 75%, 34%, and 30%, respectively, with a median survival time of 26.0 months
Botsa 2017 (16)	71	71	RFA [35]	70 [46–82]	Metastases from NSCLC	33 [15–52]	18	100%	Complete ablation	Local recurrence 22.8% (8/35)	No major complication; self-limited, post-ablation syndrome in 16/99 (16.1%) of ablation sessions	Median overall survival 14.0 months (3–18 months)
			MWA [36]			35 [18–60]				Local recurrence 19.4% (7/36)		
Frenk 2018 (3)	46	38	CRA [n=30], RFA [n=12], MWA [n=9]	66 [41–80]	Metastases from RCC (n=17; 45%), NSCLC (n=10; 26%), and other primary malignancies (n=11; 29%)	28 [7–49]	37 [2–128]	NA	Partial ablation 11% (5/46); 3/5 successfully retreated with complete tumor ablation in 96% (44/46)	Local progression rate 25% (11/44), successfully treated or retreated; local progression-free survival at 1, 2, 3, and 5 years was 82%, 75%, 69% and 55%	12% of major complication (haemobilia and acute cholecystitis, n=1; hypertensive crisis with cardiac abnormalities, n=4; pneumothorax, n=1); 6% of minor complications (intermittent urinary retention, n=1; self-limited hematoma, n=1; hematuria during ablation, n=1)	1, 3, and 5 years overall survival 82%, 44%, and 34% respectively
Zhou 2018 (11)	38	33	RFA	60 [43–75]	Metastases from lung cancer (n=16), liver cancer (n=8), RCC (n=5), colon cancer (n=3), and ovarian cancer (n=1)	30 [13–85]	22.8 [3–48]	97%	Partial ablation 18.9% (7/37)	Local recurrence 24.2% (8/33); recurrence-free time 27.4 months	4.3% of severe complication (HC with acute myocardial injury n=1; massive pneumothorax, n=1); 48% of mild complication (hypertension crisis, n=9; local bleeding, n=3; minimal pneumothorax, n=2; reduced adrenal function, n=2)	NA
Yuan 2018 (33)	38	63	RFA+TACE [n=38]	54.2±9.3	Metastases from HCC	33 [15–73]	26.3 [4–66]	100%	Partial ablation 7.9% (3/38)	Local tumor progression 7/38 patients; mean local tumor progression-free survival 8.6±6.5 months	No major complications; pain, hypertensive crisis (n=6), mild hemothorax and pneumothorax (n=2), post-ablation syndrome (n=21)	1, 2, and 3 years overall survival 92.1%, 73.7%, 55.3% respectively
		25	TACE [n=25]	56.8±8.8		35 [12–81]			Partial ablation 24% (6/25)	Local tumor progression 7/25 patients, 6.4±7.3 months	No major complications; pain, post-embolization syndrome (n=13)	1, 2, and 3 years overall survival 88.0%, 64.0%, 44.0% respectively
Huang 2019 (12)	22	22	RFA	53.0±13.0	Metastases from HCC	4.0 [17–8.0]	10 [3–55]	92%	Partial ablation 22.7% (5/22)	Local tumor progression 22.7% (5/22 patients); local tumor progression rate 3, 6, and 12 months 15.8, 26.3, and 26.3% respectively	1 major complication (ventricular fibrillation); hypertensive crisis (3/22, 9%), arrhythmia (n=1)	6, 12, 24 months overall survival 79.7, 52.6, and 32.9% respectively
Welch 2011 (24)	12	12	CRA	70 [63–85]	Metastases from RCC (n=6), other malignancies (HCC, melanoma, squamous cell lung carcinoma, neuroendocrine large cell carcinoma of the lung, penile squamous cell carcinoma, urothelial carcinoma)	2.7 [1.2–4.5]	18 [3–55]	NA	Partial ablation 8% (1/12); 1 lesion retreated to complete ablation	NA	No major complications; 6/13 (46%) hypertensive crisis; 1/13 (8%) pleural effusion	NA
Zhang 2018 (34)	31	31	CRA	57.9±9.6	metastases from lung cancer (n=18), RCC (n=10), colon cancer (n=2), HCC (n=1)	3.0±0.7	30.5 [8–66]	NA	Partial ablation 9.7% (3/31); 3 patients retreated with secondary complete ablation (100%)	Local tumor progression 19.4% (6/31 patients); 1-, 3-, and 5-years local progression free survival 80.6%, 37.8%, and 18.4% respectively	No major complications; no hypertensive crisis (mild blood pressure increase n= 9), back pain (n=6)	Mean overall survival 37.1±4.2 months; 1-, 3-, and 5-year survival rates 83.9%, 45.0%, and 30.0% respectively
Wang 2009 (17)	5	5	MWA	59 [47–76]	Metastases from HCC (n=4), RCC (n=1)	34.8 [2.3–4.5]	19 [8–31]	NA	Partial ablation 20% (1/5); one lesion retreated to complete ablation	No local recurrence	No major complications; no hypertensive crisis; pain (n=4), mild pleural effusion (n=1)	one patient developed further HCC foci and bone metastases
Li 2011 (19)	10	9	MWA	54 [41–83]	1 primary ACC, 8 metastases (lung cancer=4, HCC=2, intrahepatic cholangiocarcinoma=1, osteosarcoma=1)	3.8 [21–61]	11.3 [3–37]	NA	Partial ablation 10% (1/10); one lesion retreated to complete ablation	No local recurrence	No major complications; hypertensive crisis (n=1); pain (n=1)	5/8 patients with adrenal metastases died from the progression of primary tumors or metastases to other organs
Men 2016 (20)	31	31	MWA	64.9 [45–82]	metastases from lung cancer	3.4 [1.5–5.4]	11.1 [4–32]	100%	Partial ablation 9.7% (3/31); secondary efficacy rate 66.7%	Local tumor progression 22.6% (7/31); median local tumor progression-free survival 9 months; local tumor progression-free survival rate 77.4%	5.6% (2/31) major complications; pain in 38.9% (14/36), mild hypertension, hematoma, post-ablation syndrome	Median overall survival 12 months; 1-year overall survival rate 44.3%
Shibata 2000 (26)	9	7	PEI	64 [58–72]	Metastases from HCC	3.8 [2.5–6.0]	19.3[6–36]	100%	Partial ablation 22% (2/9)	Local tumor progression 33% (3/9)	2/7 (29%) abdominal pain; 2/7 (29%) fever; 1/7 (14%) adrenal insufficiency	3 patients (42.9%) died at 8–36 months; 4 patients (57.1%) alive at 6–28 months
Xiao 2008 (25)	20	14	PEI, PAI	NA	Metastases from lung cancer (n=9), HCC (n=6), gastric cancer (n=3), RCC (n=2)	5.9 [3.1–8.6]	25	NA	NA	Complete response rate 30% (6/20), partial response rate 70% (14/20) at 24 months	No major complications except pain; no hypertensive crisis	5/14 patients (35.7%) died at 2 years due to extra-adrenal metastases
Vogl 2007 (21)	9	9	LITT	65 [58.7–75]	Metastases from colorectal carcinoma (n=5), HCC (n=1), oesophageal carcinoma (n=1), carcinoid (n=1), and RCC (n=1)	4.3 [2.0–6.1]	10 [1–22.4]	100%	Partial ablation 22% (2/9)	Local tumor progression 22% (2/9)	No complications	2 patients died due to systemic tumour progression; longest survival time 24 months

ACC, adrenocortical carcinoma; AE, arterial embolization; CRA, cryoablation; HCC, hepatocellular carcinoma; LITT, laser interstitial thermal therapy; MWA, microwave ablation; NA, not available; NSCLC, non-small cell lung cancer; PAI, percutaneous acetic acid injection; PEI, percutaneous ethanol injection; RCC, renal cell carcinoma; RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization.