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Thermal ablation in adrenal disorders: a discussion of the technology, the clinical evidence and the future

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Purpose of review
To summarise the emerging role of thermal ablation as a therapeutic modality in the management of functioning adrenal tumours and metastases to the adrenal gland.

Recent findings
Observational evidence has demonstrated the benefit of thermal ablation in (i) resolving adrenal endocrinopathy arising from benign adenomas, (ii) treating solitary metastases to the adrenal and (iii) controlling metastatic adrenocortical carcinoma and phaeochromocytoma/paraganglioma.

Summary
Microwave thermal ablation offers a promising, minimally invasive therapeutic modality for the management of functioning adrenocortical adenomas and adrenal metastases. Appropriate technological design, treatment planning and choice of imaging modality are necessary to overcome technical challenges associated with this emerging therapeutic approach.

Keywords
adrenal adenoma, adrenal tumour, Cushing's syndrome, microwave thermal ablation, primary aldosteronism

INTRODUCTION

The past decade has seen the widespread application of minimally invasive technologies to thermally ablate solid tumours within large organs, using radiofrequency electrical energy (RFA), microwave thermal ablation (MWA), cryoablation, high-intensity focused ultrasound and laser [1]. Thermal ablation has largely been applied within the clinical setting to inoperable malignancies or metastases within the liver or kidney, with more recent applications to tumours of the bone, lung and breast [2,3]. The modality is largely safe, well-tolerated and efficacious within these settings. It is usually delivered using radiological image-guidance, most commonly via Computed Tomography (CT) or ultrasound [4]. However, thermal ablation remains an emerging therapy and the majority of currently supporting evidence comes from longitudinal cohort studies. Large randomised controlled trials are lacking in the area, although important studies such as the Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases trial aim to fill this gap [5,6].

Although the clinical focus of thermal tumour ablation has been malignancy, this therapeutic modality offers exciting and paradigm-shifting potential to provide definitive therapy to benign endocrine tumours, particularly within the context of systemic endocrinopathy [7–10]. In this regard, several case series and small observational studies have examined the efficacy and safety of both RFA and MWA in the setting of thyroid, parathyroid and adrenal tumours [11]. This article focusses on the application of microwave and radiofrequency thermal ablation to the adrenal gland and provides (i) a review of the technology behind thermal ablation, (ii) an overview of its clinical use in adrenal disorders and (iii) a brief discussion of future direction.

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KEY POINTS

- Thermal therapy is a potentially viable alternative treatment to surgery for adrenal tumours, which can allow preservation of normal tissue of the gland.
- All ablation procedures of the adrenal gland require pre adrenergic blockade in order to prevent intraoperative hypertenisve crisis.
- Thermal therapy has the potential to provide a curative treatment to those patients with bilateral adrenal disease.
- Thermal therapy is generally less invasive than surgery, can provide a shorter operative time, shorter hospital stay, and provide lower complication rates.
- From the studied reviews its success in treating endocrinopathies and controlling adrenal metastases is similar to that of adrenalectomy.

BIOLOGICAL EFFECTS OF THERMAL ABLATION

The objective of thermal ablation is to produce a core tissue temperature >50°C in order to induce cell death by coagulative necrosis [12]. The principle therapeutic challenge relates to reaching a core temperature that covers the entire tumour volume, but which does not damage adjacent critical tissues or organs. In addition to coagulative necrosis within the so-called *ablation zone*, an inflammatory infiltrate is typically seen within the intervening *transition zone* between the area of effective ablation and adjacent healthy tissue (Fig. 1) [13]. Immune infiltrates of monocyte/macrophages, neutrophils, dendritic cells, natural killer cells, and lymphocytes have all been demonstrated within the transition zone across varying tissue types following both RFA and MWA [14]. Interestingly similar immune infiltrates have also been described in metastatic deposits remote from the ablated tumour site, as well as within the circulating blood following ablation [13,15]. Several mechanisms have been proposed for this response including the effect of tumour ablation to cause a local release of damage associated molecular patterns, such as heat shock proteins and HMGB1. When released extracellularly, these molecules act as chemoattractant chemokines that stimulate a local and sometimes systemic immune response [16]. The immune response to thermal ablation is an exciting area of research and is hypothesised to play a role in modulating spontaneous regression of distant tumour metastasis following ablation of a primary tumour or metastatic lesions [17]. Tumour specific T cell responses observed following thermal ablation therapy have been associated with increased tumour-free survival in humans [18]. Supporting data for this association, generated in animal models demonstrate resistance to graft re-growth in animals subjected to a tumour rechallenge following previous thermal ablation [17]. Tumour immunoediting is an interesting feature of thermal ablation that offers the potential for systemic augmentation with immune therapy in order to maximise patient outcomes.

THERMAL ABLATION: TECHNOLOGY AND APPROACH

Systems for delivering RFA and MWA are both illustrated in Fig. 1. Briefly, both systems use an energy generator to transmit electrical or microwave energy at varying doses via an applicator probe to a tissue targeted for thermal ablation. Conversion to thermal energy occurs at tissue-level and relies upon tissue properties, such as water content (MWA) and electrical impedance (RFA). Applicator probes are usually rigid, although flexible applicator designs are also available [19]. Probes are typically guided to their target tissue/tumour through an introducer needle using radiological image guidance via CT or ultrasound. Pulsed (RFA) or constant (MWA) energy is delivered to the target over a period of 5–20 min, with the aim of reaching a core temperature >50°C within the targeted tissue or tumour, delivered over a cumulative time period of 4–5 min.

Although the general principle of delivering thermal energy to a targeted tissue or tumour is similar between both systems, the technology and the manner of heating differs considerably. Radiofrequency has traditionally been more commonly utilised within the clinical setting, yet MWA offers several advantages and the technology to effectively and precisely deliver MWA has recently advanced. An illustration of the heating patterns for RFA and MWA is provided in Fig. 2 and a comparison of both modalities is provided in Table 1 [4].

Radiofrequency ablation has principally been used to target hepatic tumours. However, the past decade has seen its indications expand to other organs/tissues. Temperatures ranging between 60 and 100°C are generated at the applicator tip, via alternating current, at frequencies from 100–500 kHz. Effective RFA requires that targeted tissue has low electrical impedance. Consequently, RFA is limited technically by the following: (i) heating is only achieved immediately adjacent to the applicator and (ii) high temperatures at the applicator tip dehydrate tissue, increases electrical impedance and hinders energy penetration into circumjacent tissue [19]. This is typically overcome by delivering pulsed

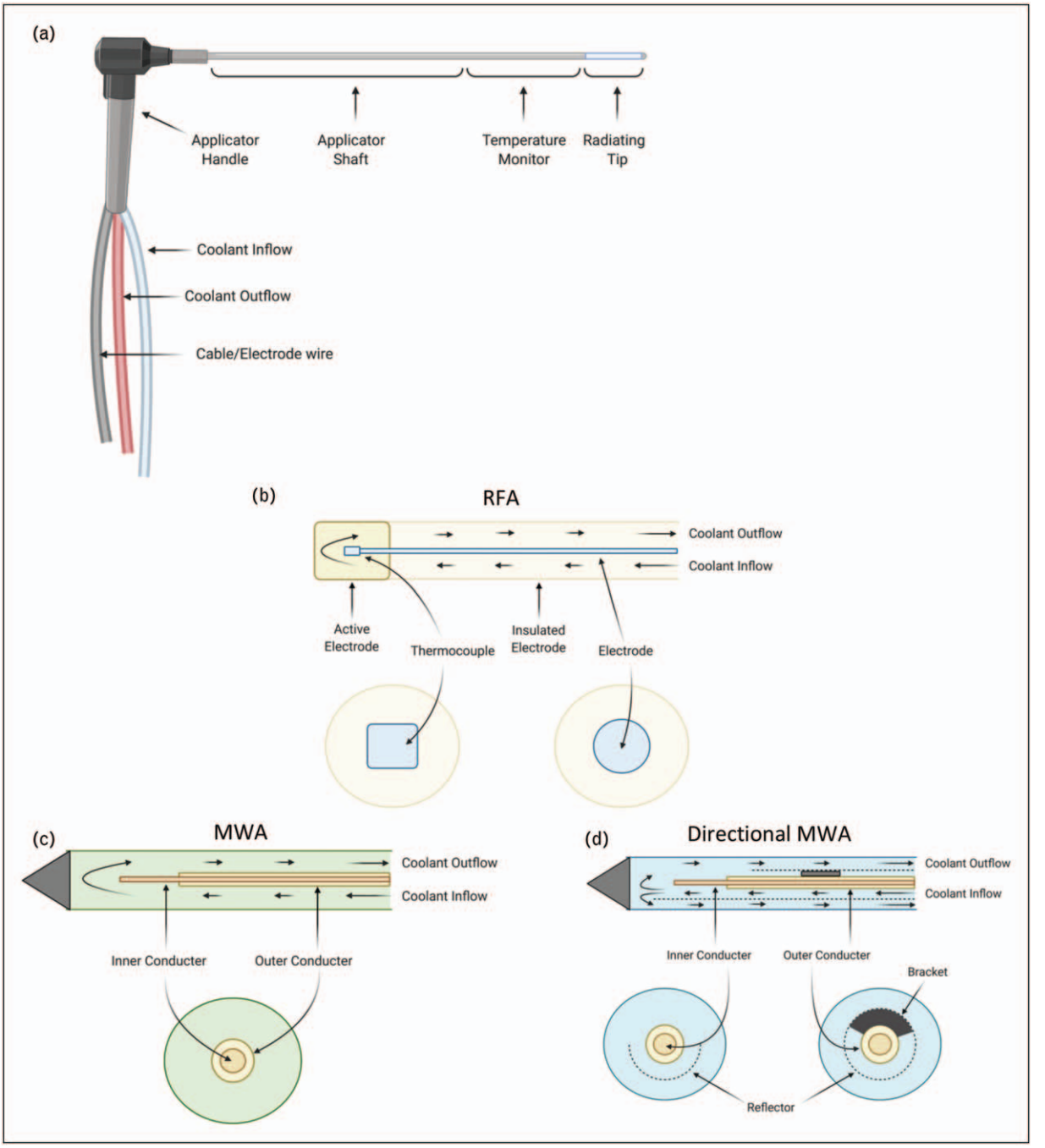

FIGURE 1. Ablation probe components; (a) General ablation probe components. All ablation probes have the same general setup which includes cables/wires leading from a generator, along with cooling inflow and outflow tubes from a peristaltic pump. The applicator shaft consists of an insulated portion and ends at the radiation tip from where hyperthermia is induced. The cross section of the ablation probes (b), (c), and (d) show while probes look similar externally, their internal components vary considerably.

RFA over a more prolonged duration in order to achieve sufficient penetration. Challenges of tissue penetration are further compounded by heat sink, whereby applied temperatures are reduced by adjacent large blood vessels absorbing heat and carrying it away through the effects of blood flow, thereby decreasing the hyperthermic efficiency of RFA [20].

MWA produces heat through electrical hysteresis. It provides better tissue healing and efficiency when compared to RFA and is less susceptible to heat sink. An electromagnetic field between 900 and 2500 MHz is delivered to targeted tissues via a coaxial cable. This field causes polar molecules (usually water) to constantly realign with the oscillating

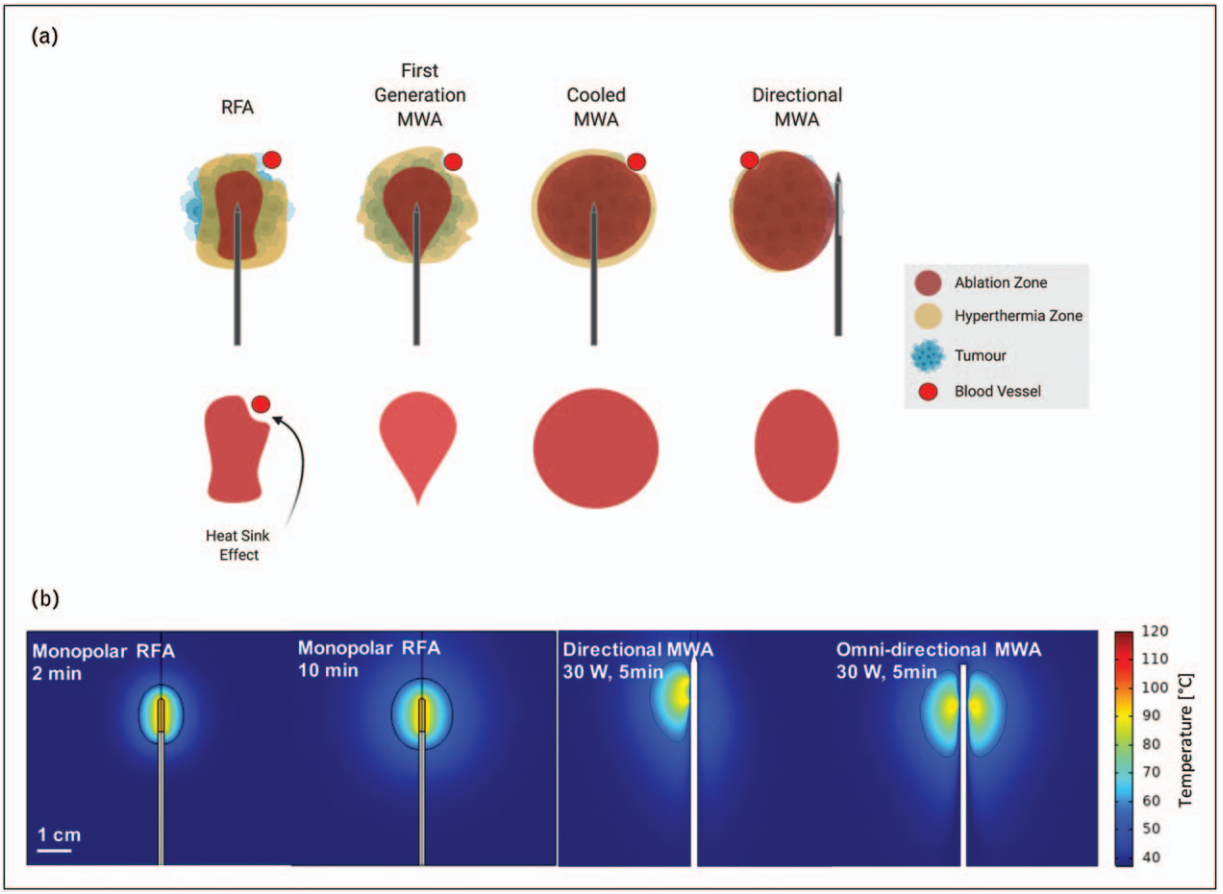

FIGURE 2. Ablation probe heating patterns; (a) This illustration depicts the general heating pattern demonstrated by each modality and the effects of proximal vasculature. (b) Mathematical models can be used to predict heating patterns for each modality and device in adrenal tissue. The simulations illustrate thermal profiles following ablation with a 15 G monopolar RF applicator with a 10 mm active electrode following 2 and 10 min heating. The applied RF power was adjusted to constraint temperature at the electrode - tissue interface within the range 90–97°C. MWA simulations are for a 14 G water-cooled directional applicator and a 15 G water-cooled omni-directional MWA applicator [39]. Both MWA applicators operate at 2.45 GHz and simulations are shown for 30 W power delivered to the applicator for 5 min. Simulation figures courtesy Faraz Chamani, Austin Pfannenstiel, Punit Prakash. MWA, microwave ablation.

Table 1. Differences between radiofrequency ablation (RFA) and microwave ablation (MWA)

	RFA	MWA
Heating mechanism	Results in hyperthermia via electric current which relies upon tissue conductivity and ion content. (–)	Results in hyperthermia via electromagnetic energy which relies upon tissue polar molecule (water) content. (+)
Grounding pad	Requires the use of grounding pads which can result in burns (–)	Does not require grounding pads (+)
Heating efficiency	Inefficient at higher temperatures due to tissue desiccation resulting in increase impedence (–)	Rapid heating and little effect of tissue desiccation(+)
Heat sink	Heat sink effect can be a major issue for well vascularised organs (–)	Less susceptible to heat sink (+)
Procedure time	More procedural time (–)	Less procedural time (+)
Ablation volume	Smaller ablation sizes (–)	Larger ablation sizes(+)
Ablation zone	Unpredictable (–)	Predictable, allowing for better treatment planning (+)
Procedural pain	Higher level of pain (–)	Less level of pain (+)

Advantages (+), Disadvantage (–).

electric field. Molecular rotation increases kinetic energy that is converted to heat within targeted tissues. Heat conductance using this modality favours tissues with a high percentage of water such as solid organs and tumours [21,22]. Microwave systems typically provide better tissue penetration compared to RFA as they do not require paths of low electrical impedance [23]. They can also produce larger, more precise, spherical ablation zones within a shorter application time, using constant rather than pulsed energy delivery [24▪▪,25▪▪,26▪]. Multiple synergistic antennae can also be synchronously used to deliver focused energy to single large tumours or even to simultaneously target multiple tumour loci [27].

Microwave however is not without its challenges. Generation and transmission of microwave energy have traditionally been difficult to achieve and must be carried in coaxial cables, which of wider gauge than that of the simple wires used in RFA applicators [28]. Cable heating presents a greater challenge for MWA, when compared to RFA and therefore these systems must be cooled, using water or gas, both of which add to the complexity and diameter of the applicator antennae [22,25▪▪,28, 29▪▪,30,31]. It is due to these complexities that the advancement and broader use of MWA in the clinic have lagged behind RFA [32].

ADRENAL TUMOURS AND THE ROLE OF THERMAL ABLATION

Tumours of the adrenal gland have an estimated prevalence of 3–10% in the population aged >50 years and are commonly picked up as so-called incidentalomas on abdominal imaging [33]. Overall, 80% of adrenal incidentalomas are of no clinical significance [34]. For the remaining 20%, surgical resection/adrenalectomy is the definitive treatment of choice where indicated [35–38] The following tumours of the adrenal gland are typically resected: (i) benign functioning unilateral tumours associated with systemic endocrinopathy[39]; (ii) adrenocortical carcinoma (ACC) [38]; (iii) phaeochromocytoma [40]; (iv) solitary metastasis to the adrenal gland [41](Table 2). Bilateral functioning tumours of the adrenal are usually not amenable to resection due to the lack of widespread, feasible options for adrenal sparing surgery compounded by the difficulty in identifying and localising specific hyperfunctioning regions within the adrenal [42]. Uncommonly, where severe systemic endocrinopathy is driven by disease in both glands, bilateral adrenalectomy is undertaken [43,44]. However this involves a considerable prognostic trade-off between patient-specific implications of endocrinopathy, which must be balanced with the inevitable complication of lifelong adrenocortical insufficiency [36].

Adrenalectomy, where possible, represents the current treatment of choice for definitive management of adrenal disease. In this regard the approach to adrenalectomy has advanced considerably over the past two decades [45]. Laparoscopic adrenalectomy is now the surgical technique of choice, with some centres offering retroperitineoscopic approaches [46]. Although not widely available, adrenocortical sparing surgery has also been undertaken for bilateral disease localised within the adrenal [46,47]. Nonetheless, adrenalectomy remains a skilled surgical procedure, requiring general anaesthetic within an often high-risk population and representing the resource-intensive costs associated with hospitalisation, operating room use and the personal and economic implications of the recovery period.

Thermal ablation of the adrenal gland may overcome some surgery associated challenges. This percutaneous and minimally invasive technique offers the potential for fast and effective therapy to disrupt adrenal tumours while reducing patient discomfort, cost and hospitalised days [48▪▪]. Its indications are additionally broadened to those unwilling or unfit for adrenalectomy due to co-morbidity [49]. It is in this regard that thermal therapy has been trialed amongst small cohorts as a (i) minimally invasive alternative to definitive management of benign adrenal adenomas [39,50–56], (ii) adrenal metastases in patients unsuitable for surgery and [3,10,48▪▪,57–59] (iii) for local management of metastatic adrenal cancers [60▪▪,61▪▪,62,63▪▪].

Advancement of thermal ablation of the adrenal gland through specifically designed precision application systems provides the opportunity to selectively disrupt localised, diseased tissue within one or both adrenal glands while leaving nontargeted adjacent normal tissue unaffected - thereby minimising the risk of postprocedural adrenocortical insufficiency [24▪▪]. This makes thermal therapy a potentially paradigm shifting candidate for definitive management of unilateral adrenal tumours, as well as offering an exciting option for definitive management of endocrinopathy driven by bilateral localised adrenal disease [24▪▪]. However, significant progress must be made in terms of applicator design and generation of clinical evidence before these clinical applications can be introduced in a safe and consistent manner.

ADRENAL ABLATION: CURRENT CLINICAL EVIDENCE

Current evidence supporting thermal ablation of adrenal disorders arises from small observational

Table 2. Previous literature of adrenal thermal ablations and their outcomes

Author	Year	Ablation	Tumour	Size	Patient No.	Residual	Recurrence	Biochemical Resolution	Complications	Follow Up
Arima *et al.* [51]	2007	RFA	Adenoma, Cushing's	2.0–3.5 cm	4			100%	Hypertensive crisis (25%), Pneumothorax (25%)	46 months
Nishi *et al.* [52]	2012	RFA	Adenoma, Cushing's	3 cm	1			100%	Adrenal hypofunction which recovered after 18 months	5 years
Chini *et al.* [3]	2004	RFA	Metastasis to adrenal	2.8 cm	1	100%			Severe hypertension (249/140 mm Hg) and narrow complex tachycardia (140 bpm).	
Frenk *et al.* [57]	2017	RFA, MWA, Cryo	Metastasis to adrenal	<5 cm	38	4%	24%		Hypertensive Crisis (57%), Intermittent urinary retention (6%), Acute cholecystitis (2%), Pneumothorax (2%),	37 months
Hasegawa *et al.* [58]	2015	RFA	Metastasis to adrenal	1.2–8.2 cm	35	6%	23%		Acute Renal Failure (3%), Heart Failure (3%), Hypertensive Crisis (66%), Hepatic hematoma (3%)	30.1 months
Liu *et al.* [48▪▪]	2020	RFA	Metastasis to adrenal	1–9 cm	29	24%			Ascites (3.5%), Pain (28%), Ventricular fibrillation (3.5%), Hypertensive crisis (13.7%), Bradycardia (3.5%)	24.5 months
Wolf *et al.* [64]	2012	RFA, MWA	Metastasis to adrenal	2–8 cm	19	5%	15% after first ablation, 5% after second ablation			14 months
Mendiratta-Lala *et al.* [53]	2010	RFA	All Neoplasm, (APA, cortisol-secreting. testosterone-secreting)	<3.2 cm	13			100%	Hypertension (15.4%), Adrenocortical insufficiency recovered after 15 months (8%)	41.4 months
Mayo-Smith *et al.* [11]	2004	RFA	All Neoplasm (metastases, PA, APA)	1–8 cm	12	15.4%			Retroperitoneal hematoma (8%)	11.2 months
Abbas *et al.*	2013	RFA, Cryo	APA	1.5–2.5 cm	5			60%	Hypertensive crisis (100%)	12 months
Liu *et al.* [39]	2016	RFA	APA	1.6 cm	24			96%	Pneumothorax (4.2%), Retroperitoneal hematoma (12.5%)	21.2 months

Table 2 (*Continued*)

Author	Year	Ablation	Tumour	Size	Patient No.	Residual	Recurrence	Biochemical Resolution	Complications	Follow Up
Liu *et al.* [10]	2016	RFA	APA	1.5 cm	36			92%	Pneumothorax (8%), Retroperitoneal hematoma (8%), Infected retroperitoneal hematoma (3%)	6.2 years
Sarwar *et al.* [55]	2016	RFA	APA	<4 cm	12			Cured hypertension (17%), Fewer antihypertensives (58%)		463 days
Szejnfeld *et al.* [56]	2015	RFA	Conns and Cushings Syndrome	1.5–3.4 cm	11			100%		24 months
Delijou *et al.* [62]	2018	RFA	Metastatic PPGL		21				Hypertensive Crisis (4.8%), Post ablation bleeding (4.8%), argon gas embolism (4.8%)	
Kohlenberg *et al.* [63▪▪]	2019	RFA, Cryo	Metastatic PPGL	5.5 cm	31 patients, 123 lesions, 80 lesions examined		14%		Pain, fever (14%), Gastrointestinal bleeding (3.2%), Hypertensive crisis (14%)	60 months
Fintelmann *et al.* [59]	2016	RFA, MWA, Cryo	Metastasis to adrenal	0.7–11.3 cm	57				Hypertensive crisis (43%), Adrenal insufficiency (22%), Ventricular tachycardia (1.4%)	
Ren *et al.* [68]	2016	MWA	All Neoplasms (metastases, cortical adenomas, pheo)		33		15.2%	100%		24 months
Liu *et al.* [60▪▪]	2019	RFA	ACC	6.3 cm	1					12 month
Veltri *et al.* [61▪▪]	2020	RFA, MWA	ACC	14–43.5 cm	16		21.8%		Intrahepatic hematoma (6.2%)	42 months

ACC, Adrenocortical carcinoma; APA, aldosterone producing adenoma; Cryo, cryoablation; MWA, microwave ablation; PA/PGL, pheochromocytoma/paraganglioma; RFA, radiofrequency ablation.

clinical studies and case series using RFA, MWA and cryoablation (Table 2). These studies have documented short and intermediate term outcomes for unilateral aldosterone producing adenomas (APA) [8,39,50,53,55,56], cortisol secreting adenoma [51–53], Adrenocorticotropic Hormone-dependent Cushing's disease [53,56], adrenal metastases and pheochromocytoma [60▪▪,61▪▪,62,63▪▪]. The approach to ablation has not been consistent across all studies and definitions of clinical response to therapy vary in accordance with underlying pathology [30–47,48▪▪]. For malignancy and metastasis to the adrenal, success is determined by change in tumour characteristics on imaging, specifically (i) tumour-size reduction, (ii) absence of local tumour progression or (iii) progression/recurrence-free survival [11,48▪▪,51,57,58,63▪▪,64]. For APA, phaeochromocytoma and Cushing's syndrome, success is additionally determined by biochemical resolution/improvement of endocrinopathy and resolution of hypertension [51–54,65]. In spite of the inhomogeneity of treatment approach and lack of standardised outcome reporting, the current data are encouraging in support of adrenal ablation. A summary of specific studies in which adrenal ablation has been applied is provided in Table 2.

Outcomes for biochemical resolution of endocrinopathy in the setting of unilateral APA, or cortisol-secreting adenoma is high for studies using both RFA and MWA. In general, all studies have demonstrated cure of endocrinopathy in both settings for 75–100% of cases after a single ablation and 100% following repeated ablation. For APA, complete resolution of hypertension occurs in approximately 45%, with complete or partial resolution in 90% following thermal ablation. This is comparable with unilateral adrenalectomy [8,39,51,52,66,67].

For metastases to the adrenal gland, both MWA and RFA have demonstrated high efficacy of tumour ablation, demonstrating postprocedural presence of residual tumour in fewer than 25%, with similarly low recurrence rates (<25%). Overall survival rates have not been evaluated due to the lack of a comparator and the heterogeneity of the underlying primary malignancy in these studies [3,48▪▪,57,58,64,68].

Staged, bilateral RFA was undertaken in a small case series of 5 patients with severe Adrenocorticotropic Hormone-dependent Cushing's disease, unresolved following hypophysectomy. In all patients, there was a resolution of hypercortisolaemia, as well as Cushingoid clinical features following ablation. However, there is no long-term follow-up of disease recurrence [69]. Adrenal thermal ablation of phaeochromocytoma has had variable success. Hypertensive crisis (HTC) arising from tumoral degranulation of stored catecholamine remains a high risk and adrenalectomy remains the unquestionable treatment of choice [62,63▪▪,70].

METASTATIC CANCERS OF THE ADRENAL

Localised therapy is now recommended for the management of metastatic tumour bulk in patients with ACC [71]. Evidence for this approach is evolving for metastatic adrenal malignancy, albeit that it is a well-healed modality for disease control in other malignancies [12]. Most recently, a single case series of 16 patients has described efficacy of CT-guided RFA to the liver and lung for oligometastatic ACC. The results of this study are encouraging, reporting radiological evidence of complete ablation in 97% of targeted lesions. Local progression was low and occurred in larger lesions, with an overall rate of 24% and a median local progression-free survival of 21 months [61▪▪]. Single case studies have demonstrated efficacy of this approach for spinal metastasis from ACC [60▪▪]. Similarly, localised therapy has been used to treat metastatic deposits from phaeochromocytoma/paraganglioma (PGGL), not fully controlled with chemotherapy or Peptide Receptor Radionuclide Therapy alone [62,63▪▪]. A recent case series described the outcomes of 31 patients with metastatic PGGL all of whom were alpha blocked for 7–14 days prior to ablation and treated with a combination of RFA, cryoablation or ethanol injection. Ablation of metastasis to bone, liver and pelvis achieved local control in 74–94%. Tumour progression was reported in 6–26% (median time to progression 16 months). Symptoms related to catecholamine excess also improved in patients treated using this modality and procedural HTC was reported in 14% [62,63▪▪].

The data for both indications are promising and demonstrate the efficacy of palliative ablation of metastases arising from adrenal malignancy in experienced hands. However, ablating metastases within large organs is the traditional indication for thermal ablation and the indication for which currently approved technology has been optimised. This is in contrast to thermal ablation to the adrenal gland itself, which remains challenging.

COMPLICATIONS

HTC, arising from medullary degranulation represents the greatest risk of adrenal ablation irrespective of cortical or medullary aetiology [24▪▪,57,63▪▪]. The risk for medullary degranulation and transient catecholamine crisis is highlighted by two studies in swine that demonstrated transient hypertension and catecholamine crisis with respective use of

MWA and RFA to ablate normal adrenal glands. Catecholamine crisis occurred even when limited ablation of a small adrenal volume $<1\,cm^3$ was undertaken with minimal medullary destruction, indicating the risk for widespread medullary degranulation even in the presence of limited and localized insult [24▪▪,72]. These findings have been borne out in human studies where HTC is demonstrated in as high as 57% of individuals undergoing ablation [57]. HTC is frequently accompanied by ventricular arrhythmia in the setting of catecholamine excess [48▪▪]. In studies using preprocedural alpha adrenergic blockade, rates of HTC are reduced significantly for ablation of adrenocortical lesions (Table 2) [63▪▪]. Therefore, peri-procedural alpha blockade should be routinely undertaken for all thermal ablation procedures to the adrenal gland. Additionally, adrenal ablation should only be undertaken following firm biochemical diagnosis of the underlying lesion. Specifically, ablation of large primary phaeochromocytomas should reserved for exceptional conditions, where gold-standard therapeutic approach is not possible. and performed following adequate preprocedural alpha adrenergic blockade and with periprocedural anaesthetic support. HTC mandating procedural stoppage and emergency pharmacological intervention adversely impacts patient safety and therapeutic outcome, as well as carrying significant health economic implications [40].

Technical complications and structural damage are slightly higher for adrenal ablation when compared to ablation in other organs, due to the narrow window of approach [33]. These include pneumothorax [39,51,54,57], haemorrhage, vascular thrombosis and visceral perforation [11,39,54,58,61▪▪,62,63▪▪] (Table 2). Where patients with Cushing's syndrome have been treated, adrenocortical insufficiency, as expected has occurred [53]. Pain is a common minor complication of RFA that requires anaesthetic or sedation, and occurs less frequently with the use of MWA [5].

TECHNICAL CHALLENGES AND IMAGE-GUIDED APPROACHES

Ablation of the adrenal gland remains a highly skilled procedure and presents greater technical challenges for the operator when compared to hepatic or renal ablation [33]. Most currently available thermal ablation technology is not engineered with adrenal therapeutics in mind. At present, approved RFA and MWA delivery systems are engineered to treat malignancy within large organs, aiming to ablate large tissue volumes, i.e., targeted tumour plus margins [5,19]. The adrenal is a small gland, affected predominantly by benign adenomas. Ideal application of adrenal thermal ablation should aim to (i) selectively ablate the offending tumour, while (ii) avoiding nearby critical structures and simultaneously (iii) preserving adjacent normal adrenal, thus minimising the risk of adrenocortical insufficiency and peri-procedural hypertensive catecholamine crisis. To optimally achieve these therapeutic outcomes mandates the specific design of appropriate applicator antennae [24▪▪].

Current image-guidance for adrenal ablation favours CT fluoroscopy over ultrasound [33]. This imaging modality offers clearer visualisation of the adrenals and critically also identifies adjacent structures, such as lung, colon and major vessels e.g. the splenic artery and the inferior vena cava. Ultrasound does not provide adequate resolution of the adrenal nor the surrounding structures to safely inform probe placement for adrenal ablation [73]. Moreover, ultrasound imaging is further hampered by steam generation during the thermal ablation procedure itself [74]. Nonetheless, some investigators have advocated an approach to the left adrenal gland using endoscopic ultrasound [75]. During CT fluoroscopy, patients are placed in the prone or ipsilateral decubitus position [48▪▪,76]. The former provides the largest approach window and minimises the contact between the adrenal and adjacent organs. The latter reduces respiratory excursion of the diaphragm and reduces the transpleural path, thereby minimising the risk for pneumothorax [77]. Hydrodissection can be used in order to increase the space between the targeted adrenal and adjacent critical structures [78]. Advance treatment planning between the interventional radiologist and endocrinologist is recommended in order to inform the optimum approach with will maximise therapeutic efficacy and patient safety.

FUTURE DIRECTIONS FOR THERMAL ABLATION OF ADRENAL DISORDERS

Thermal ablation, as a therapeutic approach to adrenal tumours is in its infancy and does not yet represent a feasible routine alternative to gold-standard adrenalectomy. High quality supporting evidence for the use of adrenal ablation is not yet available and as such randomized controlled trials and direct head-to-head comparisons with surgery are necessary to fully evaluate its benefit. Undoubtedly thermal ablation offers promise to increase the scope for delivery of definitive therapy for adrenal endocrinopathies in unilateral and perhaps bilateral disease [24▪▪,69,79]. However, significant challenges remain in the development of the technology. Current off-the-shelf ablation systems need to undergo

design modifications to facilitate safer approach to the adrenal and to provide precision selective ablation of adrenal adenomas. Recent animal studies suggest that side-firing probes may offer superior precision for ablation of adrenal lesions [19,21,24▪▪,25▪▪,26▪,28,29▪▪,31,80].

Development of precision treatment planning systems is also necessary. This should incorporate the following (i) high resolution structural imaging, to inform the window of approach [64]; (ii) functional [42,81] imaging, to identify the intra-adrenal target and (iii) preprocedural computerized simulation [22] of thermal ablation pattern, to inform the dose and duration of ablation. Many of the elements to develop proper treatment planning exist, such as high resolution structural imaging and simulators. However, reliable functioning imaging of adrenocortical lesions remains a challenge, and modalities such as 11C Metomidate PET/CT are not widely available [42,81].

The management of metastatic lesions arising from adrenal malignancy is also an exciting area for further investigation. The immune editing capability of thermal ablation has not been studied in this context specifically for adrenal disease. However, emerging data in other malignancies have demonstrated regression of multiple remote metastases following thermal ablation of a single lesion [82]. A possible mechanism for this effect is the marked change in the immunological milieu of these metastases, which demonstrate a change in monocyte/macrophage polarization and a lymphocyte infiltration [17]. It has been suggested that in this regard, thermal ablation may increase the sensitivity of therapy resistant metastases to immune checkpoint inhibitors [83]. This represents an exciting prospect for investigation in the context of improving treatment response to immune therapy for lymphocyte poor ACC [84].

CONCLUSION

In summary, thermal ablation of adrenal disease, while in its infancy shows promise but requires significant evidence generation to support its use. With technological advance and improved systems for treatment planning, this modality offers potential to shift the paradigm whereby we approach definitive management of adrenal endocrinopathy, as well as improving the prognosis and overall survival of patients with widespread ACC and PGGL.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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