Eur Radiol
DOI 10.1007/s00330-006-0516-7

UROGENITAL

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Adrenal metastases: CT-guided and MR-thermometry-controlled laser-induced interstitial thermotherapy

Received: 16 December 2005
Revised: 22 June 2006
Accepted: 20 October 2006

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Abstract The aim of the study was to evaluate the feasibility, safety and effectiveness of CT-guided and MR-thermometry-controlled laser-induced interstitial thermotherapy (LITT) in adrenal metastases. Nine patients (seven male, two female; average age 65.0 years; range 58.7–75.0 years) with nine unilateral adrenal metastases (mean diameter 4.3 cm) from primaries comprising colorectal carcinoma (n=5), renal cell carcinoma (n=1), oesophageal carcinoma (n=1), carcinoid (n=1), and hepatocellular carcinoma (n=1) underwent CT-guided, MR-thermometry-controlled LITT using a 0.5 T MR unit. LITT was performed with an internally irrigated power laser application system with an Nd:YAG laser. A thermosensitive, fast low-angle shot 2D sequence was used for real-time monitoring. Follow-up studies were performed at 24 h and 3 months and, thereafter, at 6-month intervals (median 14 months). All patients tolerated the procedure well under local anaesthesia. No complications occurred. Average number of laser applicators per tumour: 1.9 (range 1–4); mean applied laser energy 33 kJ (range 15.3–94.6 kJ), mean diameter of the laser-induced coagulation necrosis 4.5 cm (range 2.5–7.5 cm). Complete ablation was achieved in seven lesions, verified by MR imaging; progression was detected in two lesions in the follow-up. The preliminary results suggest that CT-guided, MR-thermometry-controlled LITT is a safe, minimally invasive and promising procedure for treating adrenal metastases.

Keywords LITT · Adrenal metastases · Laser ablation · Minimally invasive therapy

Introduction

The adrenal gland is a common site of metastatic disease. The incidence of adrenal metastases found at autopsy is 8.6–27% of all malignancies [1, 2]. Adrenalectomy and laparoscopic partial adrenalectomy are the standard treatment for adrenal masses [3–5] and provide effective management of adrenal metastases [6, 7]; however, the risks involved in surgery, such as bleeding or inflammatory complications, are significant. The trend towards minimally invasive options in the management of adrenal tumours has prompted the development of other therapeutic modalities, such as selective arterial embolization, percutaneous injection of alcohol and acetic acid into the tumorous lesion, radiofrequency ablation (RFA), microwave thermotherapy, and laser-induced interstitial thermotherapy (LITT) [8–10], all designed to destroy tumour tissue. LITT is a minimally invasive technique involving the placement of laser catheters into the tumours, followed by thermal ablation of targeted lesions by the application of laser energy. It has become an accepted therapy in solid organ disease. The advantage for thermal destruction of the adrenal gland tumour is the minimally invasive character. Thus, the risk of bleeding, infection or injuries of adjacent organs is reduced. Targeted tumour tissue is destroyed by coagulation necrosis when tissue temperature has reached 55°C. Numerous applications have been reported, including the treatment of primary and metastatic liver tumours

[11, 12], benign prostatic hyperplasia [13], breast cancer [14], osseous metastases [15] and renal cell carcinoma [16]. The purpose of our prospective study was to assess the feasibility of CT-guided MR-thermometry-controlled LITT for adrenal metastases and to evaluate the preliminary results.

Materials and methods

Patients

From May 2002 to January 2005, nine consecutive patients (seven male, two female; mean age 65 years; range 58.7–75 years) with nine unilateral adrenal metastases of primary malignancies comprising colorectal carcinoma (n=5), hepatocellular carcinoma (n=1), oesophageal carcinoma (n=1), carcinoid (n=1), and renal cell carcinoma (n=1) underwent prospective CT-guided, MR-thermometry-controlled LITT. The LITT procedure was approved by our Institutional Review Board, and informed consent was obtained from all patients before the laser treatment was performed and before other treatment options, possible side effects and complications were discussed. All nine patients had unilateral adrenal lesions, five on the right side and four on the left side. The mean diameter of the adrenal mass was 4.3 cm (range 2.0–6.1 cm). Prior to laser therapy all lesions were confirmed as metastases, by MR imaging (n=3) or CT-guided biopsy (n=6). All patients had received LITT for liver metastases or lesions of the primary tumour, and, via LITT, complete control of the liver involvement had been achieved. The patients developed the adrenal metastases during the follow-up period, between 6 months and 2 years after successful treatment of the liver.

Procedural protocol

LITT was performed with an Nd:YAG laser with a wavelength of 1,064 nm (Dornier MediLas 5100, Dornier, Germering, Germany). The laser light was delivered through fibre-optic bundles, terminated by a diffuser. The diffuser was mounted at the end of a 10 m long, 400 µm-thick silica fibre core to emit laser light to an effective distance of 12–15 mm. The diameter of the diffuser tip was 1.1 mm. This laser fibre was inserted into an internally cooled laser application system. The active length of the diffuser tip was adjusted to the size of the lesion and was either 2 cm or 3 cm. The power of the laser was 10–12 W per centimetre active length of the diffuser tip.

A power laser application system (Somatex, Teltow, Germany) was used for LITT treatment. This laser application system consisted of a cannulation needle, a sheath system, and a protective catheter that prevented direct contact of the laser applicator with the treated tissues, enabling complete removal of the applicator, even in the unlikely event of damage to the fibre during treatment. The protective catheter was 7-F in diameter and was internally cooled with a room-temperature sodium chloride solution that circulated within a double-lumen catheter. Cooling the surface of the laser applicator modifies the radial temperature distribution. This shifts the point of maximum temperature towards deeper tissue layers, hence enlarging the coagulation necrosis.

LITT

After localization of the tumour using CT imaging, we positioned the irrigated power laser application system under sterile conditions using CT guidance (T.V.). The patients were either in the supine or lateral position, depending on the optimal access. Small lesions (≤1 cm) were treated with one laser applicator system; for larger lesions (>1 cm) up to four laser application systems were inserted so that we could obtain larger areas of coagulation necrosis. This was calculated according to the maximum distance of 20 mm for the position of the laser applicators next to each other. Thereafter, the patients were transferred to the adjacent MR room.

The LITT treatment was performed under MR guidance using a 0.5 T scanner (Privilege, Elscint, Israel) by T1-weighted gradient echo (GE) sequences [TR/TE 140/12 ms, flip angle 80°, matrix 128 pixels × 256, pixels field of view (FoV) 250 mm, five slices, slice thickness 8 mm, interslice gap 30%, acquisition time 15 s] in axial slice orientation and parallel to the laser applicators (T.V., M.M.). These two sequences were repeated every minute, allowing near-online monitoring of the laser ablation. The position of the laser fibres and the laser power were readjusted according to geometry, signal intensity, and speed of heat distribution. Previous clinical studies have demonstrated that a temperature increase of ≥80°C results in a visible loss of signal intensity [11]. The laser application was stopped after coagulation of the lesion had been confirmed in the MR images. Contrast-enhanced T1-weighted sequences were subsequently performed to visualize the immediate effect of the ablation. After completion of the procedure, the puncture channel was closed with fibrin glue (Tissucol Duo S 2 ml Immuno; Baxter, Vienna, Austria).

The entire LITT treatment took on average 80 min and was performed using local anaesthesia, intravenously injected analgesics and sedatives in the following doses:

Local anaesthesia and intravenously injected analgesics: pethidine 10–80 mg (Dolantin, Aventis Pharma, Frankfurt, Germany), and/or piritramide 5–15 mg (Dipidolor, Janssen-CILAG AG, Neuss, Germany).

Sedative: (2–10 mg midazolam, Hoffmann–La Roche, Grenzach-Wyhlen, Germany). Local anaesthesia was achieved with 20–30 ml of 1% mepivacaine (Scandicaine, AstraZeneca GmbH, Wedel, Germany). All necessary precautions for hypertensive crisis were taken. Although only rare complications have been reported after biopsies or other manoeuvres on the adrenal gland, the patients were intensively monitored.

MR imaging

Unenhanced and contrast-enhanced [0.1 mmol/kg body weight gadolinium diethylene triamine penta-acetic acid (Gd-DTPA), Magnevist, Schering, Berlin, Germany] MRI was performed in all cases so that we could verify the necrosis obtained. The imaging protocol included a T2-weighted breath-hold turbo-spin echo (TSE) sequence (TR/TE 3,000/92 ms, matrix 154 pixels × 256 pixels, flip angle 150°, slice thickness 4 mm) in transverse slice orientation, a half-Fourier single-shot turbo-spin echo (HASTE) sequence (TR/TE 1,000/60 ms, matrix 178 pixels × 256 pixels, flip angle 147°, slice thickness 4 mm), and a T1-weighted unenhanced and contrast-enhanced GE sequence [combined Gd-DTPA per kilogramme body weight (bw), Magnevist, Schering) [fast low angle shot (FLASH) 2D, TR/TE 110/5 ms, matrix 178 pixels × 256 pixels, flip angle 90°, slice thickness 4 mm] in transverse and sagittal slice orientation. The first follow-up MRI study was performed on the day after the LITT treatment. Further follow-up studies were performed every 3 months after the intervention. All follow-up studies were performed on a 1.5 T scanner (Symphony Quantum, Siemens, Erlangen, Germany).

Image evaluation

Local tumour control was evaluated for all metastases that had been treated with the irrigated power laser application system. Images of tumours and surrounding parenchyma obtained before and after laser treatment were compared with each other and with those obtained in follow-up examinations. Unenhanced and contrast-enhanced MR images were used for follow-up studies by the same technique as described above. Areas that were not enhanced by contrast medium were considered to represent necrotic tissue [17–20]. Recurrent tumour at the ablation site was defined by the following criteria: the volume of the lesion had increased compared with that at the examination 3 months earlier; parts of the lesion showed a bulge consisting of solid material with contrast enhancement. Furthermore, the sizes of the metastases and the size of the coagulation necrosis were measured in three dimensions. All evaluations were performed by two radiologists (T.V., M.M.). The decision was made by consensus.

Tumour volume and volume of coagulation necrosis were calculated on the basis of measurements in three dimensions. The three greatest dimensions (referred to as x, y, and z) were then used to calculate the volume of an ellipsoid [$(4\pi/3)(x/2)(y/2)(z/2)$] [21].

Local tumour control was determined using unenhanced and contrast-enhanced MR images obtained 3 months, 6 months, and 12 months after LITT treatment.

Results

All patients tolerated the puncture and the CT-guided, MR-thermometry-controlled LITT treatment well, under a moderate amount of systemic analgesics and local infiltrative anaesthesia. No complications occurred during and after the laser treatments. Technical success was achieved in all tumours with a single therapy session.

The qualitative evaluation of the change in signal intensity during the MR monitoring for thermometry revealed a rapid loss in signal intensity in all lesions in the first 3 to 5 min, followed by a slower decrease in signal intensity. The maximum achieved signal loss in the metastases was equal in all patients. After the maximum signal loss had been achieved, LITT was regularly performed for three more minutes and then stopped. The time for LITT ablation was in a range between 15 min and 22 min. The mean number of applicators per lesion was 1.9 (range 1–4). A successful placement of the laser applicators was achieved in all tumours. The mean applied laser energy was 33 kJ (range 15.3–94.6 kJ).

The mean diameter of the laser-induced coagulation necrosis was 4.5 cm (range 2.5–7.5 cm), and the mean volume of the coagulation necrosis was 38.8 cm^3 (range 4.9–102.3 cm^3) (Fig. 1).

The mean follow-up time after LITT treatment was 10 months (range 1 month to 22.4 months). Complete ablation was achieved in seven lesions, verified by MR imaging, with no signs of residual enhancement on the follow-up contrast-enhanced MR images (Fig. 2). Thus, the local tumour control rate was calculated to be 78%. Two lesions showed tumour progression on MR imaging 5 months and 6 months after treatment, respectively (Fig. 3).

Seven patients were still alive at the time of this evaluation. Two patients had died during follow-up 9 months and 20 months after the intervention due to general tumour progression. The longest survival time so far has been 24 months.

Discussion

Metastases of malignant neoplasms to the adrenal gland are frequent. At autopsy, 8–38% of patients with extra-adrenal malignancies have metastases to the adrenal glands [22]. Adrenal metastases may be unilateral or bilateral, and they are almost always clinically silent. The most common primary malignancies to metastasize to the adrenal gland are lung, kidney, breast, or gastrointestinal carcinomas. Recently, the detection rate of clinically silent adrenal

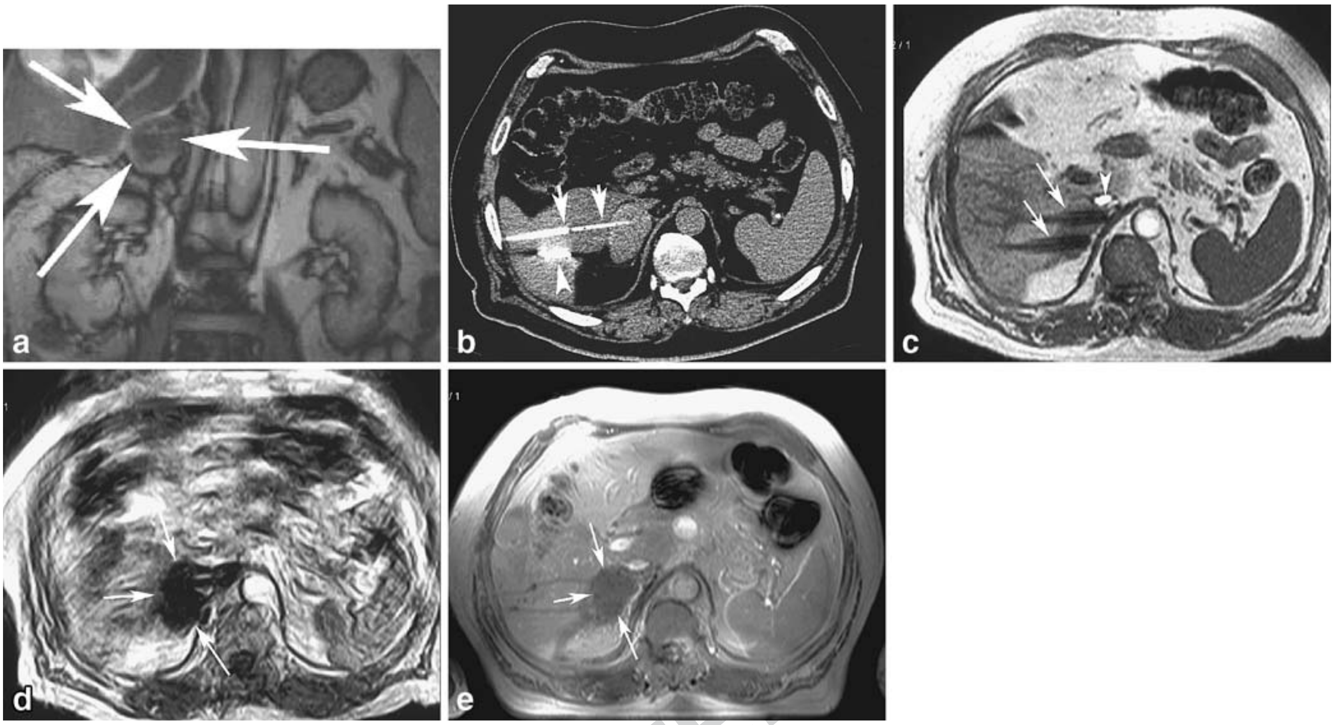

Fig. 1 Right adrenal metastasis of colon carcinoma in a 68-year-old woman. **a** Coronal T2-weighted SE sequence MR image (TR/TE 1,000/60 ms; flip angle 147°) obtained 2 weeks before LITT shows a right adrenal tumour (*arrows*) with central heterogeneous hypointense structure. **b** Transverse CT fluoroscopic image obtained during the trans-hepatic insertion of the laser applicator system demonstrates one laser applicator in the right adrenal tumour (*arrows*) and the needle for puncturing (*arrowhead*) during insertion of the second applicator system. **c** Transverse T1-weighted gradient-echo MR image (TR/TE 140/12 ms; flip angle 80°) obtained immediately before LITT demonstrates two laser applicators (*arrows*) placed in the adrenal tumour via a magnetite marker. Note the position close to the inferior vena cava (*arrowhead*). **d** Transverse T1-weighted gradient-echo MR image (TR/TE 140/12 ms, 80° flip angle) obtained during LITT (8 min after the laser ablation had been started) shows signal loss in the areas of the adrenal tumour (*arrows*). Note the image artefacts due to thermal effect and breathing movement of the patient. **e** Transverse contrast-enhanced T1-weighted gradient-echo MR image (TR/TE 110/5 ms; flip angle 80°) obtained 6 months after LITT shows no enhancement of the treated right adrenal metastasis and complete devascularization

lesions has increased, due to the widespread use of abdominal imaging modalities [1, 2]. Siemer et al. [23] reported that adrenal metastases of primary renal cell carcinoma were found in 5.5% of patients and more often in patients with an advanced tumour stage. Nakashima et al. [24] found in their study the presence of adrenal metastases in 8.4% of 225 patients with hepatocellular carcinoma (HCC) at autopsy.

Adrenal lesions can be divided into two major categories: functional and non-functional. They occur in 9% of the population [25, 26]. Incidental detection of adrenal lesions commonly occurs in up to 5% of patients when abdominal CT is used [26–29]. Metastases tend to be larger than adenomas, have an irregular shape of heterogeneous density and a thick, irregular enhancing rim after intravenous administration of contrast medium [28]. Lesions greater than 4 cm in diameter tend to be either metastases or a primary adrenal carcinoma.

Adrenal metastases are usually fast growing and often rupture into the retroperitoneum when they become large. Early treatment of these lesions is required for disease control, and some authors have reported that successful surgical resection improves survival in certain clinical settings [6, 7, 30]. Kim et al. [6] showed that adrenalectomy for solitary, resectable lesions will contribute to prolonged survival; the overall 5-year survival rate was 24%, with a median time of 21 months. Thus, it is possible that local tissue ablation might also be beneficial for some specific clinical situations.

Imaging-guided local tumour ablation with heat energy (such as RFA, laser) offers a minimally invasive and safe treatment option. Some authors have reported the use of RFA to treat primary and metastatic disease involving the adrenal gland. Mayo-Smith and Dupuy [9] reported using CT-guided percutaneous RFA to treat 13 adrenal masses in 12 patients, 11 of which masses were metastases. The results showed that 11 of 13 lesions were treated successfully with RFA after one session. Only two large adrenal lesions (4 cm and 8 cm in size), associated with residual tumour after one treatment session, had to be treated repeatedly. No patient with metastases had recurrences at the treated site. Wood et al. [31] reported

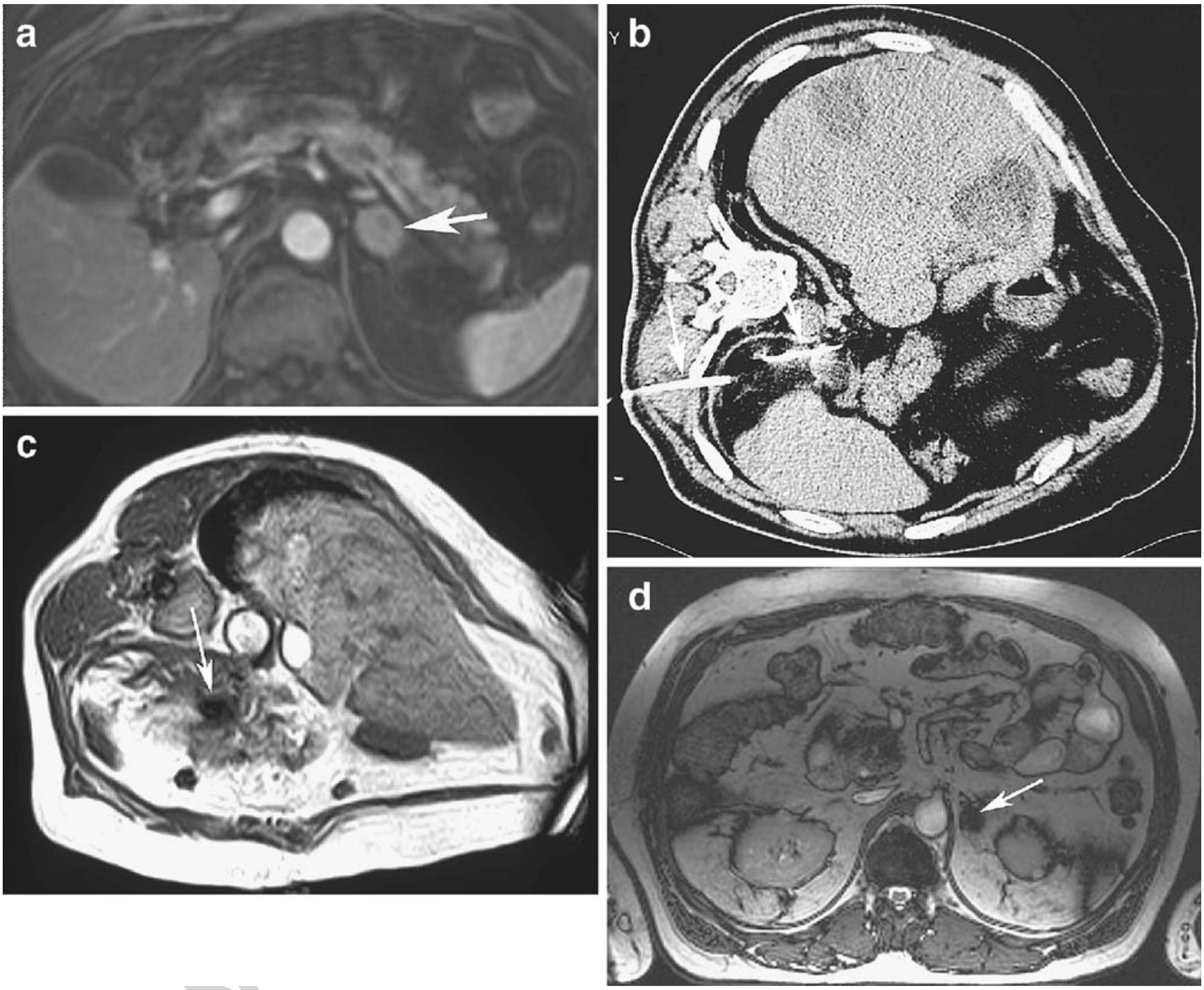

Fig. 2 Left adrenal metastasis of oesophageal carcinoma in a 61-year-old man. **a** Pre-interventional transverse contrast-enhanced T1-weighted gradient-echo MR image (TR/TE 140/12 ms; flip angle 80°) shows a left adrenal metastasis measuring 2.1 cm with enhancement (*arrow*). **b** Transverse CT fluoroscopic image obtained during the insertion of the laser applicator system with the patient in a left lateral position shows one laser applicator (*arrows*) that was positioned in the adrenal tumour dorsally; the second applicator already placed is visualized from the anterior. Note two hypointense liver lesions, which had been treated successfully via LITT 2 years previously. **c** Transverse T1-weighted gradient-echo MR image (TR/TE 140/12 ms; flip angle 80°) obtained during LITT with the patient in a left lateral position shows signal loss in the lesion due to the increase in tissue temperature (*arrow*) (15 min application time, 30 kJ). **d** Transverse contrast-enhanced T1-weighted gradient-echo MR image (TR/TE 110/5 ms; flip angle 80°) obtained 24 months after LITT shows no residual contrast enhancement of the treated lesion and no change in size (*arrow*). In the treatment follow-up the topography of the adrenal gland changed

using RFA treatment for 15 primaries and metastatic adrenal tumours in eight patients. In eight of 15 (53%) lesions a post-treatment loss of enhancement was observed and the lesions had stopped growing on follow-up CT scan after 6 months. Three of 15 lesions demonstrated interval growth, and four did not change in size. For smaller tumours with a mean maximum size less than or equal to 5 cm, eight of 12 (67%) were completely ablated, as defined by decreasing size and complete loss of contrast enhancement. Three of 15 (20%) related RFA lesions had nearly completely disappeared on imaging. Wood et al. considered RFA to be effective for the short-term local control of small adrenal tumours and most effective for tumours less than 5 cm.

LITT is a minimally invasive therapy for destroying tumours within solid organs, which conducts laser light energy into a tissue through optic fibres [32, 33]. Nd:YAG laser light with a wavelength of 1,064 nm is well suited for penetrating deep into soft tissue. Technical developments improved the application, so that the cooling of the surface

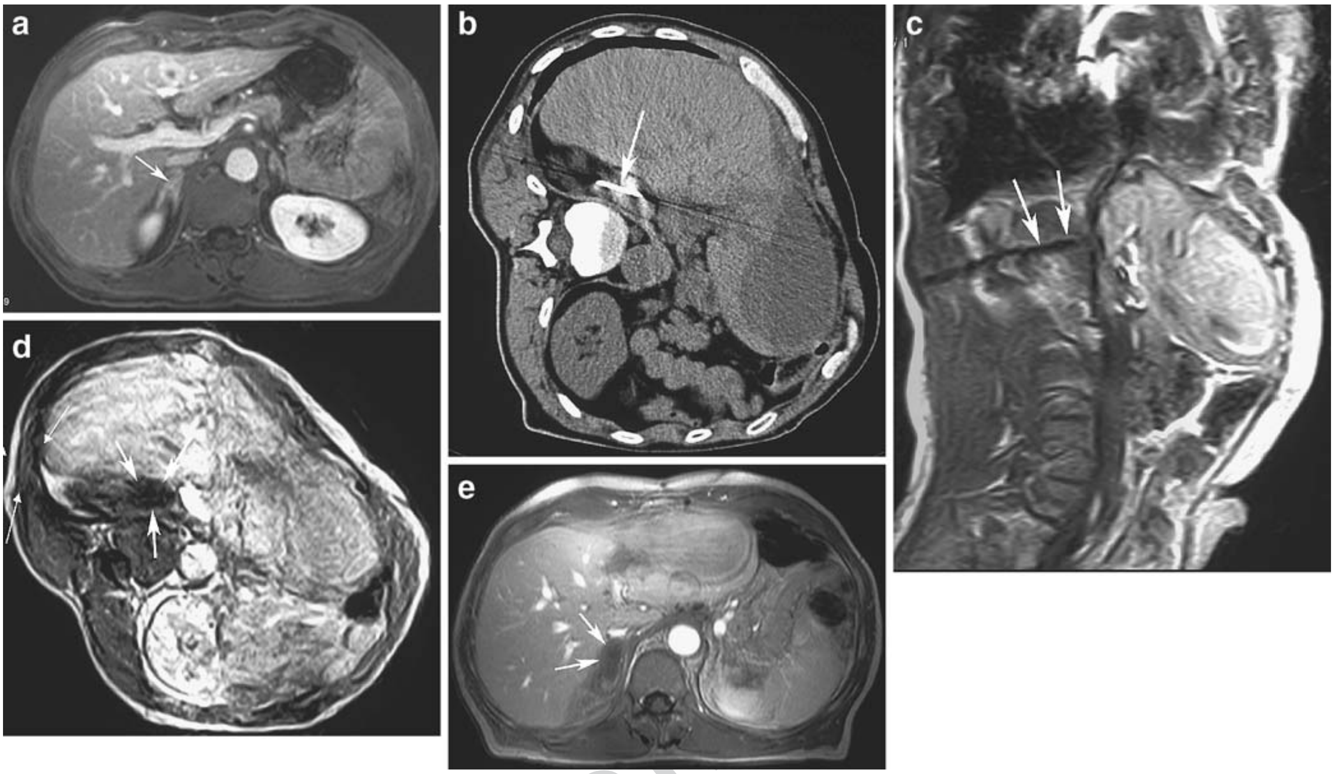

Fig. 3 Right adrenal metastasis of renal cell carcinoma in a 64-year-old man. **a** Transverse contrast-enhanced T1-weighted gradient-echo MR image (TR/TE 140/12 ms; flip angle 80°) obtained 1 month before LITT shows a right adrenal metastasis with enhancement (*arrow*). **b** Transverse CT fluoroscopic image obtained during the insertion of the laser applicator system with the patient in a right lateral position shows one laser applicator (*arrow*), which was positioned in the adrenal mass. **c** Sagittal unenhanced T1-weighted gradient-echo MR image (TR/TE 108/8 ms; flip angle 80°) obtained immediately at the beginning of LITT shows one laser applicator (*arrows*) placed in the adrenal mass dorsally. **d** Transverse T1-weighted gradient-echo MR image (TR/TE 140/12 ms; flip angle 80°) obtained 24 h after LITT with the patient in a left lateral position shows the laser- induced coagulative necrosis areas (*arrows*). **e** Transverse contrast-enhanced T1-weighted gradient-echo MR image (TR/TE 110/5 ms; flip angle 80°) obtained 12 months after LITT still shows the induced coagulative necrosis (*arrows*)

of the laser applicator and the radial temperature distribution were optimized, and the maximum temperature shifted into deeper tissue layers [32] produced an ellipsoid form of necrosis; the length of the ellipsoid depends on the length of the diffuser fibre. The volume of the laser-induced tissue necrosis depends on the laser power, the optical and thermal properties, the laser irradiation time, wavelength of light involved and the types of tissue characteristics [11]. Inserting multiple laser applicator systems and simultaneous heating can produce larger coagulative necrosis areas. Current laser techniques are proposed to treat tumours less than 5 cm in diameter [34]. It has been reported [34] that the use of a water-cooled fibre with a single applicator produced a 3 cm coagulation lesion; if two or more applicators were used in parallel fashion, lesions of 6.5 cm in size might be produced. The lesion size may be further enlarged by the use of multiple applicators during the same procedure. In our study we found that one laser applicator system produced a maximum necrosis of 3.3 cm, and two applicator systems produced a maximum necrosis of 7.5 cm in diameter.

Magnetic resonance imaging is a promising imaging modality for controlling laser ablation of adrenal metastases and has several advantages: MR imaging provides topographic accuracy with excellent soft-tissue contrast and high spatial resolution [11, 14, 35]. MR monitoring allows rapid acquisition of areas of signal loss compatible with temperature changes and, thus, real-time documentation of laser ablation effects [14, 36, 37]. The applicator position, laser power and cooling rate can be readjusted according to MR imaging during treatment. MR imaging also allows the visualization and quantification of the degree of induced necrotic lesions; and well-controlled coagulative lesions ensure treatment of the entire tumour and minimize the destruction of surrounding tissue structures. Our group demonstrated that treatment with CT-guided, MR-thermometry-controlled LITT in adrenal metastases can produce coagulative necrosis areas of up to 100 cm^3 and can result in complete ablation or can produce large areas of coagulative necrosis in the adrenal tumour. This suggests the possibility of using LITT in the treatment of adrenal metastases with a diameter of 6 cm, making it a possible alternative to surgery.

In conclusion, CT-guided, MR-thermometry-controlled LITT seems to be a safe, minimally invasive and effective therapy for adrenal metastases, with a remarkable tumour control rate. It can produce complete or large areas of coagulative necrosis in the tumour at one session, allowing effective local control in a considerable number of adrenal metastases.

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