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ARTICLE

Radiofrequency ablation of pulmonary tumours: current status

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Abstract

Radiofrequency ablation (RFA) for thoracic tumours has emerged as a minimally invasive therapy option for primary and secondary lung tumours and has gained increasing acceptance for pain palliation. The procedure is well tolerated and the complication rates are low. RFA provides the opportunity for localized tissue destruction of limited tumour volumes with medium and long term follow-up data suggesting that survival figures do parallel those of non-surgical treatment modalities. The purpose of this article is to review the status of RFA in lung tumours, to emphasize its place in symptomatic palliation and to discuss its potential role in conjunction with radiation or systemic therapy.

keywords: *Lung cancer; lung metastases; complications; pain palliation; thermal ablation; radiofrequency.*

Introduction

Radiofrequency ablation (RFA) is a rapidly expanding method for effectively treating small volume lung tumours in non-surgical candidates. Experimental studies have evaluated the feasibility and safety of percutaneous RF ablation of normal pulmonary tissue in rabbits[1] and have assessed its effectiveness in the destruction of experimentally induced lung malignancies[2–4].

Since the first case report was published in 2000 describing three patients treated for lung lesions[5], more than 120 original articles, review articles and case reports have been published in major journals worldwide covering well over 1000 patients ablated for primary or metastatic thoracic disease with curative or palliative intent.

This emerging development in interventional radiology is very exciting, but challenging as well, and it is mandatory to standardize the terminology and reporting criteria[6].

This article reviews the current status of RFA in lung tumours with additional comments on its role in pain palliation, and its potential role in conjunction with radiation or systemic therapy is discussed.

Technical features

Each RFA system consists of three components: a generator (the source of electromagnetic energy), an active electrode (placed into the target tissue and depositing the energy), and grounding pads (to dissipate the returning current). Current generators function in the range of 400–500 kHz, 1200–2000 mA and 15–200 W. Electrodes differ in size (14–17 G, 10–25 cm in length) and type (multitined expandable, internally cooled, perfused); they come singly or as cluster electrodes and have rigid, semi-flexible or fully flexible shafts. The grounding pads are placed equidistant from the ablation site, usually on the patient's thighs, in order to avoid the entire current returning to one single grounding pad and causing skin burns.

Rapidly alternating current is deposited into the target tissue, causing ionic oscillation and subsequently frictional heat. The algorithm of energy deposition is device specific; some are temperature-based and others are impedance-based. Pulsing techniques can be employed to amplify energy deposition, along with the use of adjuvant agents (concomitant instillation of sodium chloride or chemotherapeutic drugs). All these different techniques have the common aim to raise the

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temperature in the target tissue to between 60 and 100°C to induce coagulation necrosis while sparing the surrounding healthy tissue from thermal damage.

Lung tumours are usually approached percutaneously, under computed tomography (CT) guidance. Ultrasonography (US) guidance is reserved for tumours infiltrating the pleura.

Magnetic resonance (MR) is expensive and of limited availability; few electrodes to date are MR-compatible. Electrode positioning under MR is also more cumbersome, unless performed on an open magnet. Furthermore, it is not as easy to monitor pneumothorax development with MR imaging and many drainage catheters are not MR compatible. However, MR imaging may play a role in the evaluation of treatment efficacy[7–9], as it has been shown to visualize histopathologic changes after RFA and accurately determine the extent of the necrotic lesion in a porcine lung model[10]. On-line monitoring of treatment outcome can only be performed with MR imaging, offering the option of applicator repositioning for the ablation of visible residual tumour tissue. This has been applied successfully in RFA of liver[11] and kidney tumours[12]. In the setting of thoracic tumours, MR thermometry would probably only play a role for large tumours requiring multiple overlapping ablations.

Most authors define the end point of the ablation if ground glass opacification (GGO) surrounds the ablated tumour on CT scans during and at the end of treatment. With large tumours and overlapping ablations the central portions may be easily missed resulting in failure of complete ablation despite the presence of surrounding GGO. Tumours not entirely surrounded by air may also benefit from MR thermometry.

CT is currently the imaging modality used for lung lesions, not only for targeting the tumour, but also for initial planning, monitoring the electrode during ablation (Fig. 1) and assessment of treatment response.

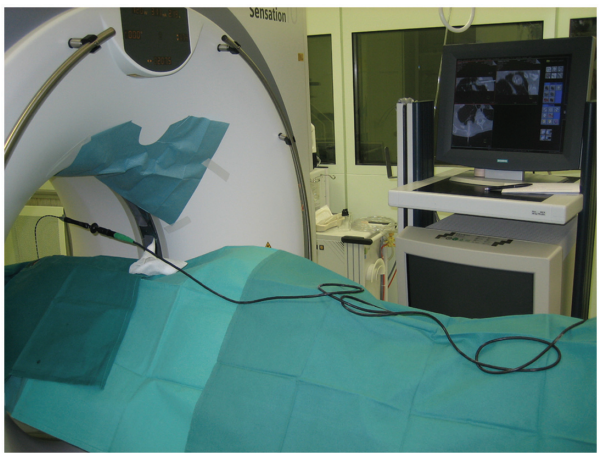

Figure 1 **CT suite during lung RFA. The electrode has been percutaneously introduced into the lung tumour and the position of the deployed tines is monitored in three planes.**

In a study comparing general anaesthesia (GA) with conscious analgosedation (AS) in the setting of ablation of lung tumours, hospitalization, complication rates and types, and the rate of local tumour control did not differ substantially between both groups. Furthermore, there was no significant difference in technical success and feasibility. The authors therefore suggest using AS for routine use, reserving GA for anxious or agitated patients[13].

Extensive data have been published showing the superiority of fluorodeoxyglucose (FDG)-positron emission tomography (PET) over CT for the staging and assessment of therapy response of primary lung cancer[14–16]; preliminary data suggest that it may have a role in assessing therapeutic efficacy and early recurrence of RF ablated lung tumours[17].

Patient selection

Patients should be selected by a joint tumour board. They are usually non-surgical candidates because of the site and distribution of their lung tumours or because of comorbidities, especially limited cardio-respiratory function. Occasionally, a patient may refuse major surgical treatment despite qualifying for it, and opt for the less invasive alternative.

Bilateral metastases can be treated, but for safety reasons only one lung a time should be ablated. Overlapping ablations are required for lesions >3.5 cm in longest diameter, however it has been shown that the size of the composite thermal injury created by overlapping multiple thermal ablation spheres is surprisingly small relative to the number of ablations performed.

Uncorrected coagulopathy is an exclusion criterion. As the treatment is elective, anticoagulation therapy should be discontinued at least 5 days prior to the intervention. The maximum acceptable number of metastases per hemithorax should be based on published data, discussed under “clinical outcome” and on common sense. The site and histological subtype of the primary tumour and the disease-free interval since treatment of the primary tumour should be considered along with size, distribution and accessibility of the nodules to RFA.

Patients who have previously undergone pneumonectomy must be considered at very high risk for RF ablation of the contralateral lung; the intervention should only be performed with thoracic surgeons and anaesthetists on stand-by and intensive care unit facilities[18].

Before treatment, a careful clinical evaluation must be performed, along with any relevant laboratory, imaging and pulmonary function tests. Pre-treatment CT of the chest is a key examination for determining the number, size and location of the lesions. Their relationship to the heart, to major bronchi and vessels must be evaluated, as well as the status of the surrounding pulmonary parenchyma. The terms of reference for post-treatment follow-up studies must also be considered.

Complications

Complications can be divided into peri-procedural and post-procedural. Peri-procedural complications are related to either needle positioning or to the ablative procedure itself.

Pneumothorax

Pneumothorax is the most common peri-procedural complication, occurring in roughly 40% of ablation sessions[19–22] and is only slightly higher than the incidence of pneumothorax post percutaneous lung biopsy, which is reported to be around 35%[23]. Factors associated with RFA-induced pneumothoraces have recently been analysed by several groups. The length of the electrode trajectory through aerated lung, the mean number of tumours ablated and the number of electrode positionings have been shown to impact significantly on the likelihood of a pneumothorax[21]. Interestingly, other high risk factors were gender, with an odds ratio of 1.84 times higher for males than for females to develop a pneumothorax, the location of the ablated tumour in the middle or lower lobe, and the lack of a history of intervention (surgery, biopsy, ablation, radiotherapy) to the ipsilateral hemithorax[20,21]. Patients with background emphysema developed a pneumothorax nearly twice as often, with an incidence of 67%[20].

Around 10% of the patients with pneumothorax require chest tube placement[20–22,24]. In these patients, the pneumothorax developed rapidly, with the estimated size of the pneumothorax usually exceeding 35%, or the patients were symptomatic[21]. Manual aspiration of the pneumothorax should be considered as a valuable option, both for safe continuation of the ablative process avoiding an excessively large RF ablation in an atelectatic lung or to ablate a tumour that had moved too close to the hilum. It may also prevent the need for insertion of a chest tube[20,25,26].

Intractable pneumothorax due to bronchopleural fistula (BPF) has been reported with an incidence of 0.6%[27] and has been attributed to location of lesions close to the pleura with tissue necrosis and sloughing, devascularization due to coagulation necrosis with compromise of spontaneous closure of the fistula. Squamous cell carcinoma originating from the bronchial wall with a nature of spontaneous necrosis also seems to predispose to BPF.

Pleural effusion

Pleural effusion requiring drainage or the insertion of a chest tube is reported to range between 2 and 7%[21,24,28,29]. Factors associated with development of large effusions were the use of internally cooled cluster electrodes, the proximity of the target tumour to the pleura (<10 mm), large tumour size, high maximum power and long total ablation time[21].

Small reactive pleural effusions are commonly seen, their incidence rising with the number of ablations and total ablation time; however they are not important, resolve spontaneously and can be classified as acceptable collateral damage.

Haemorrhage

Parenchymal haemorrhage, which is also related to needle positioning, occurs in roughly 8% of ablations[30,31] but is usually self-limiting and does not require further measures. Only a small proportion of patients (4%) with parenchymal haemorrhage develop haemoptysis[28]. Provided that the haemorrhage does not obscure the target lesion and the patient is not in discomfort, the ablative procedure can be continued as usual. Central lesion location is associated with a higher risk of haemorrhage[31] and a potentially lethal outcome[28], as is failure to discontinue medication with platelet aggregation inhibitors[32].

Cavitation

Cavitation should not be regarded as a complication but rather as a side effect; it is a frequent finding, occurring in 14–31% of ablations[30,33,34], usually resolving without further measures or therapy. It has been shown to occur more frequently in patients with a sub-pleural lesion, pulmonary emphysema, and those with primary lung cancer[33]. Bojarski *et al.* [34] have reported that cavitations develop significantly more often with tumours located in the inner third of the lung (75%) versus 2% in the outer third. Larger lesion size, vicinity to a segmental bronchus and using a cluster electrode were also found to favour cavitation[34]. No correlation with pleural effusion was found[33,34]. As the vast majority of patients with cavitations remain asymptomatic[30,33,34], and infection and abcess formation (Fig. 2) are regarded as rare exceptions, watchful follow-up and advice to the patients prior to discharge to return in the case of high fever, chills and malaise are considered sufficient[33].

Other complications and side effects

Peri-procedural pleuritic pain and raised body temperature (up to 38°C) are frequent side effects. The pain can usually be managed with non steroidal anti-inflammatory drugs (NSAID) and generous pain medication is encouraged to prevent impairment of breathing and ventilation and the subsequent risk of superinfection. Raised body temperature is thought to result from the release of cytokines and serum inflammatory mediators[35].

To prevent infection (stated to occur in up to 7% of procedures[36]) and/or abscess formation, some groups advocate routine peri-interventional intravenous administration of antibiotics[36,37], however this has not been widely adopted to date. Hypertonic saline-enhanced radiofrequency ablation, although very powerful and

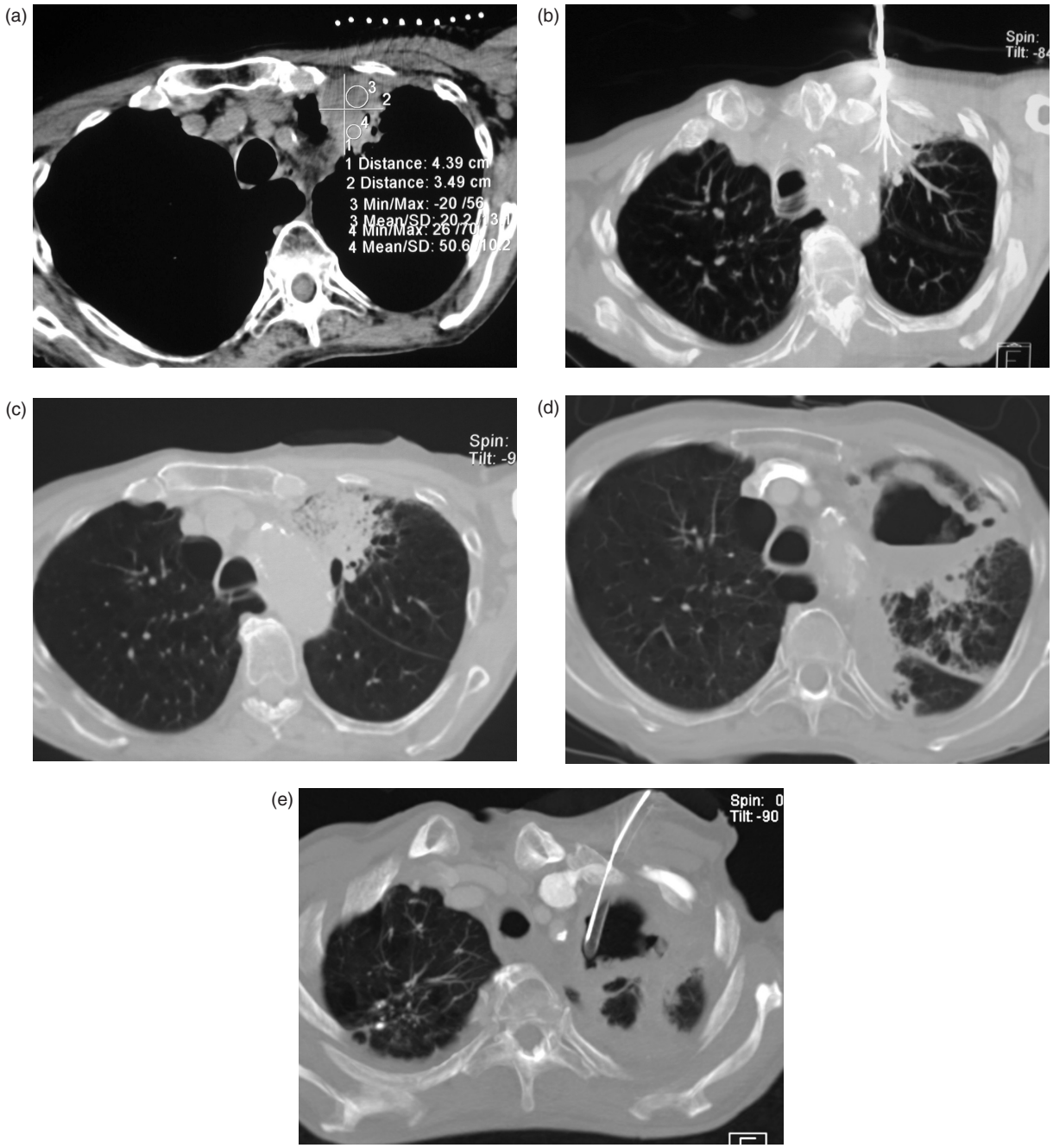

Figure 2 **(a) CT scan showing a biopsy proven recurrent squamous cell cancer post radiotherapy in the left upper lobe (LUL). (b) Electrode deployed to 4 cm. (c) Immediate post-ablative CT scan showing bubbles within the ablated tumour and an area of GGO surrounding the tumor. (d) CT scan 3 weeks post ablation shows a large cavity at the treatment site with an air-fluid level. (e) CT scan showing an inserted drain through which 250 ml of frank pus were drained.**

efficient in creating large necrotic zones, is dangerous in the lung and unpredictable due to uncontrollable dissipation of the hot saline into the tissue. This may cause excessive hyperthermic necrosis and subsequent abscess formation[38].

Malignant seeding of the needle tract is an exceedingly rare complication of transthoracic needle biopsy of lung tumours; track ablation (heating the needle track upon withdrawal of the electrode) is usually performed at the end of each ablative session and should thus even further decrease the risk of seeding. In a case report detailing malignant seeding of the needle tract, no track ablation had been performed at the end of the procedure; furthermore a biopsy of the ablated lung lesion was performed immediately prior to the ablation, therefore the seeding also may have occurred during the biopsy procedure[39].

Skin burns at the site of the dispersive electrodes have been reported[28,40]; they are usually superficial. Deeper burns have occurred due to mal-positioning of the grounding pads. In lengthy procedures and in patients with peripheral vascular comorbidities, they should be attached equidistant to the ablation site onto clean, dry, shaved skin[40].

Assessment of treatment response

CT imaging at the end of an ablative session shows an ovoid area of ground glass opacity (GGO), indicating the ablated zone with the encompassed tumour, ideally located within the centre of the GGO[30,41]. Intralesional bubbles are frequently visible in the immediate post-ablative setting (Fig. 2c); contrast-enhanced images should not show any enhancement in the completely ablated lesion[41,42], however a rim like granulation tissue surrounding the ablated centre has been shown to appear immediately post-ablation, as demonstrated in a porcine model[8]. The ablation zone should be bigger than the original tumour and will eventually reduce in size on follow-up.

The success of RFA, as defined by imaging criteria, appears to strongly correlate with the pre-treatment size of the tumour and its vicinity to the heart or large vessels. Incomplete ablation in the proximity of the heart and large vessels due to the "heat sink effect" was first described in an animal model[43], and has been reinforced by a recently published study demonstrating that local recurrence rates for ablated tumours contiguous with the heart and aorta were significantly higher than for those close (1–9 mm), but not contiguous[44].

Tumours >3 cm in longest diameter have also shown significantly higher rates of incomplete ablation/local recurrence[36,47–50]. Dodd *et al*. used a computer-assisted design system to create three-dimensional models of a spherical tumour, a spherical tissue volume consisting of the tumour plus a 1-cm tumour-free margin, and individual spherical ablations; the resulting computer analysis showed the size of the composite thermal injury created by overlapping multiple thermal ablation spheres to be surprisingly small relative to the number of ablations performed[51].

FDG-PET has an established role in the staging of primary lung cancer; it has proven to be useful in RFA for early assessment of incomplete ablation/early recurrence[17]; however, costs and availability may prevent its routine use at present.

Clinical outcome

Pulmonary RFA is still in its infancy; acceptance of the procedure as an alternative treatment option for non-operable lung tumours is quite recent. Initially, patients referred for RFA usually had advanced tumours, had exhausted radiation or chemotherapy alternatives or had severe cardiopulmonary co-morbidities, rendering them unsuitable for surgery.

Primary lung cancer

Compared to the established use of RFA for small hepatocellular carcinomas (HCC) or liver metastases, primary lung cancer tends to have a far more aggressive tumour biology compared to the hepatic counterparts. In studies with attempted curative RFA for early stage non-small cell lung cancer (NSCLC), survival data are significantly better than for the patient population treated palliatively[36,45,50]. Simon *et al*.[50] recently reported long-term survival rates after percutaneous RFA of stage I NSCLC at 78% at 1 year, 57% at 2 years, 36% at 3 years, 27% at 4 years and 27% at 5 years. These figures are superior to the survival rates from external beam radiation, showing 2- and 5-year overall survival rates of 39% and 13%[52]. It has to be emphasized that the promising survival data only apply to T1N0 stage I NSCLC. Beside the high likelihood of incomplete ablation, tumours measuring >3–3.5 cm also have a significant incidence of nodal metastases, thus FDG-PET staging prior to choosing the appropriate treatment modality should be mandatory[14–16].

Recent advances in the field of radiation therapy with hypo-fractionated high-dose proton beam therapy shows competitive survival results[53], as does stereotactic radiosurgery[54]. A combination of RFA and conventional radiotherapy has already shown better local control and survival rates than radiotherapy alone, with cumulative survival rates of 50% and 39% at the end of 2 years and 5 years, respectively[55].

No data has been published so far on the combination of RFA with chemotherapy for early stage NSCLC, however RFA combined with chemotherapy has been shown to provide a survival benefit in patients with unresectable hepatic metastases from colorectal cancer (CRC) compared with chemotherapy alone[56].

Hypoxic cells with limited blood flow, such as those found in the centre of necrotic tumours, can be resistant to chemotherapy and external-beam radiation therapy. These central hypoxic cells may be more sensitive to RF ablation because of increased cell sensitivity to heat in the hypoxic state and decreased heat dissipation due to poor tumour perfusion[57].

Lung metastases

Data on curative RFA for lung metastases show even more favourable survival numbers than for primary stage I NSCLC[36,42,58]; <5 metastases per hemithorax and a maximum diameter of 3.5 cm are felt to represent the cut-off. Lung metastases have been found at autopsy in 25–30% of all patients with malignant disease[59]. Despite nearly a third of cancer patients dying with evidence of pulmonary metastases, those patients satisfying

the criteria for surgical resection represent a much smaller subgroup.

In a retrospective study of 5206 cases undergoing pulmonary metastasectomy, 42% had sarcoma, 14% colorectal cancer, 9% breast cancer, 8% renal cancer, 7% germ cell tumour, 6% melanoma and 5% head and neck cancer[60]. Tumours exhibiting preferential spread to the lungs as the only site of metastasis include sarcoma, renal cell cancer and head and neck cancer. In contrast, tumours such as breast cancer and melanoma typically metastasize to multiple organ sites[61].

Several studies on metastasectomies have been published using heterogeneous patient populations[62–64] demonstrating that metastasectomy is safe and provides extended survival. Completeness of resection was of prognostic significance with respect to survival in all analyses. There is less agreement over the disease-free interval (DFI), tumour type, the number and size of metastases.

Surgical trauma may contribute to recurrence, growth of metastases and metastatic spread. These unwanted consequences of surgery depend on factors such as immunosuppresion[65], shedding of tumour cells into the wounded area and the circulation[66] and the production and release of growth factors for wound healing, which influence tumour cell adhesion and growth[67].

The potential advantages of local tumour destruction methods might include (a) selective damage which leads to less immunosuppresion and release of less growth factors, (b) minimal treatment morbidity and mortality, (c) less breathing impairment in patients with borderline lung function through sparing healthy lung tissue, (d) repeatability, (e) fairly low costs, (f) excellent imaging during the procedure and for follow-up, and, last but not least, (g) the gain in quality of life with less pain, much shorter hospitalization times with the interventions performed on an outpatient basis or with overnight stays and thus a quicker return to normal life.

In a homogeneous patient group treated with RFA for colorectal lung metastases, size (3 cm in longest diameter) was shown to be the only significant prognostic factor for local progression-free survival[68,69] and actuarial 1-, 2-, and 3-year survival rates were 85%, 64%, and 46%[69]. Further long-term follow-up is necessary for pulmonary metastases of primary tumours other than colorectal to determine the efficacy of RFA.

Tumour palliation

Various and impressive data are available on RFA for symptomatic osseous metastases[70–76], however it is beyond the scope of this article to discuss this in detail. VanSonnenberg *et al.*[60] reported RFA of painful thoracic tumours in 11 patients, with pain amelioration in all patients (total relief in 4, partial relief in 7); those with partial relief subjectively downgraded their pain from severe to moderate and from moderate to mild[60].

It has to be borne in mind that RFA does not strengthen bone and that a treated tumour will provide no more stability or bear more weight than a viable tumour; furthermore significant complications may result from RFA of thoracic vertebrae with posterior cortical or pedicle involvement[61]; given the high rate of success of achieving pain relief with vertebroplasty alone, an added benefit of RFA to the vertebral body has not yet been proven.

Large thoracic tumours likely to invade the thoracic wall and exulcerate (Fig. 3) might be considered for palliative ablation with the purpose of reducing tumour

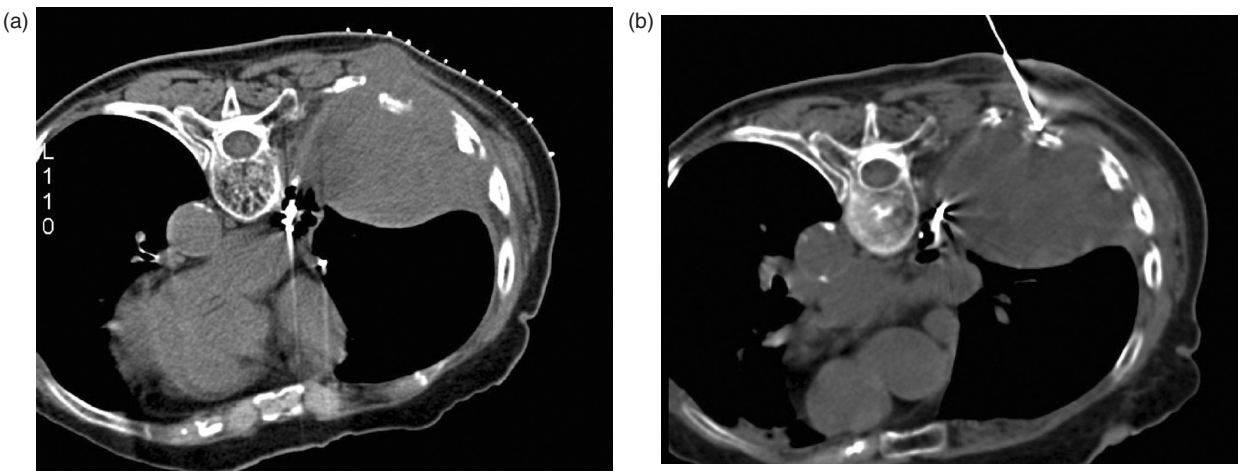

Figure 3 **(a) An 80-year-old patient with a large pleural fibrous tumour, a recurrence after two previous surgeries, and moderately painful. (b) RFA for cytoreduction to prevent the tumour from exulcerating through the skin and for pain palliation. Twenty millilitres of 20% glucose were injected into the subcutaneous space to increase the distance between the skin and the target lesion in order to avoid skin burn.**

volume and preventing or delaying associated complications.

Conclusion and future directions

Lung RFA is a minimally invasive therapeutic option for a selected group of patients with primary and secondary lung disease, requiring less resources, time, cost and recovery, and additionally offers reduced morbidity and mortality compared to surgery or radiation therapy. It is safe and technically highly successful in terms of initial ablation. Medium and long term follow-up data suggest that survival figures parallel those of non-surgical treatment modalities. Long term local control or complete necrosis rates reduce considerably when tumours are larger than 3 cm, although repeat ablations can be performed. RFA also provides a means for palliation of pain unresponsive to other therapies. With refinements in technology, patient selection, clinical applications, and methods of follow-up, RFA will continue to flourish as a potentially viable stand-alone or complementary therapy for both primary and secondary lung malignancies in standard and high-risk populations.

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