Thermal ablation in the treatment of lung cancer: present and future

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Abstract

Surgery is considered the best choice for stage I non-small cell lung cancer and also in treatment of selected patients with lung metastasis. However, surgery is often a high-risk procedure because of severe medical comorbidities affecting this cohort of patients. Thermal ablation (TA) has recently been proposed to achieve destruction of lung tumours whilst avoiding the use of general anaesthesia, thereby limiting the invasiveness of the procedure. For pulmonary malignancies, there are two methods of TA based on tissue heating: radio frequency ablation (RFA) and microwave ablation (MWA). Both are mini-invasive procedures, delivering energy to the tumour through single or multiple percutaneous needles introduced under guidance of computed tomography. The procedure may be performed under conscious sedation or general anaesthesia to avoid pain caused by needle insertion and tissue heating. Local efficacy is directly correlated to tumour target size: for RFA, tumours smaller than 2 cm can be completed ablated in 78–96% of cases; for MWA—according to the largest available study—95% of initial ablations are reported to be successful for tumours smaller than 5 cm. Very few series provide survival data beyond 3 years. For nodules smaller than 3 cm, the registered survival rate is higher: 50% at 5 years. The data collected in the last 10 years allow us to conclude that TA is an established alternative treatment for patients who cannot undergo surgery because of their compromised general condition. In the case of pulmonary metastasis, most authors agree to offer TA only if lesions are smaller than 5 cm.

Keywords: Thermal ablation • Radio frequency ablation • Lung cancer • Microwave

INTRODUCTION

Surgery is universally accepted as the best choice of therapy in stage I non-small cell lung cancer (NSCLC). This is based on the favourable outcomes, according to pathologic stage, observed in patients who have been surgically treated [1]. In the case of regional disease (stage II/IIIB) a combination of surgery, chemotherapy and/or radiotherapy (RT) is the standard protocol. The role of surgical resection for pulmonary metastasis is still being discussed: however, in the case of single nodule and specific histology, such as colorectal and kidney metastasis, surgery was found to be a safe and effective treatment method when complete resection is performed [2, 3].

However, surgery is often a high-risk procedure because of severe medical comorbidities affecting this cohort of patients [4]. Only 15% of patients with stage I/II meet the physiological criteria for parenchymal resection [5].

Therefore non-invasive local treatments that make it possible to avoid resection of functioning parenchyma or prolonged general anaesthesia represent a key point in the management of patients who are not eligible for surgery. External beam RT has been traditionally considered as the treatment of choice in these selected cases. Based on excellent results, some authors have suggested that overall survival rates after stereotactic body radiation therapy could be comparable to those following surgery [6]. However, most of the data concerning RT outcomes in terms of survival are less favourable when compared with surgery at 5 years [7].

Over the last few decades, various innovative mini-invasive therapies have been developed as alternatives to surgery. They aim to obtain tumour destruction or eradication without the use of general anaesthesia.

Among these alternative therapeutic options, thermal ablation (TA) is probably the most interesting. Initially, TA was used in the treatment of bone, kidney and liver cancer; it was introduced to lung cancer management in 2000. For pulmonary malignancies two methods, based on tissue heating, are used: radio frequency ablation (RFA) and microwave ablation (MWA).

THE ABLATIVE TECHNIQUES

The ablative technologies utilize several sources of energy and different devices to damage the target tissue. Both RFA and MWA are mini-invasive procedures, as they deliver energy to the tumour through single or multiple percutaneous needles.

RFA employs an alternating electrical current with 10–200 W of power, which is applied to the tumour via an interstitial
electrode. The flow of current leads to ion agitation, which induces tissue heating. The temperature reached is directly proportional to the current density of the tissue and is inversely proportional to distance from the electrode. When a temperature between 60 and 100°C is reached, a coagulative necrosis of the target tissue is obtained.

Different kinds of electrodes—cooled, clustered (Fig. 1) or multipolar—have been developed to increase ablation size [8]. However it is noteworthy that, independently of the needle’s characteristics, only one probe can be activated at a time, with the consequence that the duration of the procedure increases.

MWA uses electromagnetic waves at a frequency of between 915 and 2450 MHz to rapidly accelerate the rotation of the polar water molecules and obtain energy conversion into heat. MWA has several theoretical advantages over RFA, since energy is deposited over a larger active zone and higher temperatures are produced in a shorter time. Moreover MWA needle electrodes have multiple antennae functioning simultaneously, which increases the size of the ablation zone and results in the procedure taking less time than RFA.

THERMAL ABABLATION AND LUNG TISSUE

TA causes parenchymal thermal destruction without any specificity for cancer. The goal of TA is to induce targeted tissue damage by heating cells to >60°C, so as to obtain a complete necrosis of the tumour and surrounding tissue. The size of ablation achieved depends upon the unique characteristics of the tissue. In lung parenchyma, the presence of continuous bloodflow and airflow adjacent to the target is the most important factor to be considered. In particular, thermal conductivity and ‘heat sink’ effect are the main obstacles in determining the efficacy of the procedure. Thermal conductivity is lower than in other organs because of the high percentage of air, which makes it difficult to create ablations with sufficient margins. ‘Heat sink’ effect causes heat dissipation away from the target tissue due to blood- and airflow, thus limiting the intended tissue damage. These two factors influence the effects of TA and need always to be considered before deciding which nodule to treat, and the optimum ablation method.

TREATMENT PROCEDURE AND IMAGING FOLLOW-UP

TA may be performed under either conscious sedation or general anaesthesia, to avoid pain caused by needle insertion and tissue heating. Some authors have suggested a link between general anaesthesia and better outcomes, which probably correlates with the easier achievement of complete ablation [9].

Computed tomography (CT) is today the only accurate image guidance method for lung TA. It is a real-time technique and affords an adequate positioning of the needle. Additionally, CT guarantees a direct post-procedure evaluation of the ablation. Immediately after TA, the lung tumour appears to be surrounded by a ground-glass opacity, enlarging the tumour diameter (Fig. 2). It represents a zone of on-going necrosis. Ablation is considered complete if ground-glass opacity margins are present and encircle the target tumour, with a rim of at least 5 mm. Therefore ground glass opacity is an indicator of the extent of ablation achieved.

Figure 1: Patient 1: A cancer in the left lower lobe is treated by RF. The cluster needle with three lateral hooks is well visible.

Figure 2: Patient 2: after the procedure, a ground glass area around the nodule appears and guarantees the completeness of the necrosis.
Long-term follow-up for lung cancer, according to the Response Evaluation Criteria in Solid Tumours (RECIST), usually depends on changes in the diameter of the nodule visible on a CT scan. These criteria are obsolete when evaluating tumours treated with TA, as ablation zones are intended to be larger than the target itself after the treatment. Moreover it is known that tumour size increases in the first few weeks following the procedure, because of inflammation. However, contrast enhancement and its post-ablation changes may differentiate malignant from necrotic tissue.

In conclusion, CT should be performed 4–8 weeks after the ablation, to determine the baseline for future comparisons. Subsequent evaluations should show a progressive decrease in the size of the tumour, until it permanently disappears or is replaced by a scar. CT densitometry is also a valid method of determining the completeness of ablation or tumour progression.

Positron emission tomography/computed tomography (PET/CT) evaluates the metabolic activity of the tumour. It is not useful in the first weeks after the procedure, since inflammation may create false positive findings but, at subsequent follow-up, the Standard Uptake Value (SUV) of the ablated tumour is expected to decrease. Based on these criteria, PET/CT has the highest sensitivity among the available imaging techniques for the evaluation of treatment response [10].

When the ablated zone presents an increased SUV or a nodular growth in size 3 months after the procedure, a relapse has to be considered. In these cases a biopsy is recommended.

In our experience, it is useful to determine the extent of the ground-glass margins immediately after the procedure, in order to understand the effect obtained. Subsequently, follow-up is based on CT scan one month after the ablation, to obtain a baseline in size and to determine contrast enhancement. Then we use periodic PET/CT scan every 3 months to determine both local and distant disease control.

SURVIVAL

When evaluating TA results, parameters to be considered are local efficacy and survival. It is universally accepted that local efficacy correlates directly to tumour target size. For RFA, tumours under 2 cm in size can be completely ablated in 78–96% of cases [11, 12]. For MWA, according to the largest available study, 95% of initial ablations are reported to be successful in a population of 66 treatments for lung cancers of less than 5 cm [13].

Survival data for both RFA and MWA are scarce and immature, because these techniques have only been introduced for lung cancer management since the year 2000. Up to now, very few series have provided survival data beyond 3 years.

Simon [14], in a series of 75 NSCLCs treated with RFA, demonstrated a median survival of 29 months with an overall survival rate, in the first 5 years, of 78, 57, 36, 27 and 27%, respectively. A higher survival rate was registered for nodules smaller than 3 cm: 50% at 5 years.

Similar overall survival data in colorectal cancer lung metastasis has been reported by four other teams, with an overall survival rate of 64–78% at 2 years. Multivariate analysis demonstrated that, for metastasis also, a larger tumour size of over 3 cm was independently associated with a reduced survival rate ($P = 0.003$) [15].

Wolf [13] in a series of 66 MWA sessions for primary and secondary lung cancer, found that 26% of patients had residual disease, predicted by using an index size of larger than 3 cm ($P = 0.01$). Actuarial survival at 1, 2 and 3 years from ablation was 65, 55 and 45%, respectively. Survival was not affected by index size of 3 cm or by residual disease.

In our personal experience of 26 cases of lung cancer (16 primary and 10 secondary) treated with RFA, the median survival was 30 months. Survival rates at 6, 12, 24 and 32 months were 100%, 95.2%, 71.9% and 21.6%, respectively. There were relapses in every patient who had lesions larger than 3 cm, in four patients with primitive cancers smaller than 3 cm and in three patients with metastasis. Disease-free survival at 32 months divided as follows: 100% at 6, 86.3% at 12, 47.4% at 24 and 17.8% at 32 months [16].

**COMPLICATIONS**

Pneumothorax is the most common complication after percutaneous TA, with an incidence between 30–60% of the procedures [14, 15]. Usually, in asymptomatic cases, radiological control is adequate. Otherwise, patients are treated by insertion of a chest tube. We used a chest tube in 11 out of 15 cases of pneumothorax [15]. Pleural effusion is often a response to thermal injury; the percentage of cases treated by thoracentesis is usually 1–7% [17]. Seventy-eight percent of patients present self-limited parenchymal haemorrhage. Some cases of pneumonia have been reported after RFA [17]. Haemothorax is rare.

**CONCLUSION**

To date, our overview of the long-term outcomes after TA for primary or secondary lung cancer is limited as very few studies have used a homogenous population and provided survival data beyond 3 years. However, the data collected in the last 10 years allow us to conclude that TA is an established alternative treatment for patients who cannot undergo surgery because of their compromised general condition. Main indications are represented by early stage (I/IIN0) lung cancer. In the case of pulmonary metastasis, most authors agree to offer TA only if lesions are smaller than 5 cm.

Tumour size, no matter what technique is used, is a predictive factor of complete ablation, with an accepted size limit of 3 cm for both primary and secondary lung cancer.

RFA is a safe procedure, with reduced costs and short hospital stay, which guarantees a high success rate of complete ablation. This gives patients who are not eligible for surgery the opportunity of a curative treatment [18].

MWA is advantageous as it guarantees a larger ablation zone, which could lead to a better local disease control and long-term survival. The relationship between lesion size and survival needs further study but there are several early clinical studies showing interesting rates of local control, even in tumours that are larger than 3 cm.

At present, outcome data for pulmonary tumours treated by MWA are relatively scarce. There are several animal model studies that compare the effectiveness of MWA and RFA for lung cancer, which show that a larger and more circular zone of...
necrosis is obtained by use of MWA [19]. Further studies will be needed to address the optimization of TA protocols; these should include prospective randomized clinical trials comparing RFA with MWA, in order to determine the most effective technique for local tumour control. Despite the fact that some authors have presented encouraging results when comparing survival between sublobar surgical resection and TA, surgery is still the treatment of choice for early stage lung cancer [20].

PERSPECTIVE

A multidisciplinary approach is the standard treatment protocol for patients who undergo surgical resection for lung cancer, the aim being to improve outcomes by using a synergistic effect. At present, TA is mostly used as a stand-alone technique but, in the future, it will also be necessary to determine the impact of induction and adjuvant therapy in patients who have been treated by TA. Dupuy et al. reports 24 cases, treated with RFA and RT, that showed better local control and survival than with RT alone [21]. This encouraging data needs to be confirmed by multicentre trials. Further studies should aim to improve local control and survival using TA associated with other conventional local or systemic treatments.

The management of locoregional recurrences after RFA is a topic recently proposed by Lanuti et al. [22]. His paper reports different local, regional and distant recurrences, treated with repeated RFA, RT, CT or CT/RT. This data suggests that treatment for recurrences should be managed, based on an accurate evaluation of the tumour’s distinctive features. The distinction between incomplete ablation, local relapse and systemic disease should be the rationale to determine a salvage therapy. More data about treatment for recurrences are requested in future.

Some authors have proposed RFA for symptom palliation in thoracic cancer. Some interesting data are available on the treatment for painful thoracic tumours involving the chest wall [23]. Another field of interest is the treatment of symptomatic osseous metastasis. We have also suggested the use of RFA in the management of recurrent haemoptysis due to unresectable lung cancer [24]. These experiences suggest that tumour palliation could further enlarge the use of percutaneous thermal ablation in thoracic oncology.

Conflict of Interest: none declared.

REFERENCES