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Anti-Tumour Treatment

"Review of current thermal ablation treatment for lung cancer and the potential of electrochemotherapy as a means for treatment of lung tumours"

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ABSTRACT

Lung cancer remains the most common cancer diagnosed worldwide and has one of the lowest survival rates of all cancers. Surgery remains the only curative treatment option but because most patients are either diagnosed at advanced stages or are unfit for surgery, less than a third of all lung cancer patients will undergo a surgical resection. Thermal ablation has emerged as an alternative option in patients who are unfit to undergo surgery. Thermal ablative therapies used in clinical practice to date include Radiofrequency Ablation (RFA), Microwave Ablation (MWA) and Cryoablation This article will focus on the advantages and limitations of thermal ablative therapy and investigates the potential of a relatively new treatment modality, Electrochemotherapy (ECT), as a novel treatment for lung cancer.

Introduction

Lung Cancer is the most common cancer diagnosed worldwide with 1.3 million cases newly diagnosed ever year. It has one of the lowest survival rates of all cancers since more than two thirds of cases are diagnosed at an advanced stage.[1] The 5 year relative survival rate is only 11.2%.[2] Lung cancer accounts for 6% of all deaths and 22 % of all deaths from cancer.[3] Surgical resection remains the gold standard of therapy in early stage Non-Small Cell Lung Cancer (NSCLC), being the only therapeutic option with proven long-term cure and survival. Surgery is usually reserved for only stages I–II of the disease, which represents only a small portion of lung cancer patients as two thirds of cases present at an advanced stage.[1] Even if a patient's cancer is deemed operable, factors such as co-morbidities or poor underlying lung reserve can preclude any major surgical intervention. It is estimated that over 20% of patients with early stage disease do not undergo surgical intervention because of their comorbidities.[4] The current surgical resection rate in the United Kingdom is only about 14% in proven NSCLC cases,[1] whilst the resection rate in North America is about 21%.[5]

Thermal ablation has recently been advocated as an alternative treatment, especially in patients with early stage disease who are not surgical candidates. The principle modalities in clinical practice to date are Radiofrequency Ablation (RFA), Microwave Ablation (MWA) and Cryoablation This article will focus on the advantages and limitations of thermal ablative therapy and investigates the potential of a relatively new treatment modality, Electrochemotherapy (ECT), as a novel treatment for lung cancer.

Radiofrequency ablation

Basic principles

Radiofrequency ablation uses a high frequency current to heat and coagulate tissues.[6] An alternating electrical current of usually 500 kHz with a power of up to 200 W is applied to the target lesion by means of an electrode. The current moves from the active electrode in the target lesion to grounding pads placed on the patient and back to the active electrode. This alternating current movement causes the ions in the tissues to oscillate, resulting in friction and heat.[7] At temperatures between 60 °C to 100 °C, protein denaturation takes place, leading to coagulative necrosis.[8] Temperature beyond 105 °C results in excessive charring and desiccation of

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tissues which increases impedance and decreases the electrical current flow.[9] Therefore, the therapeutic range for RFA is quite narrow; between 65 °C and 105 °C.

Pre-clinical data and early experience with RFA in lung tumours

Radiofrequency ablation has been mostly investigated in the setting of liver tumours both in animal and human clinical studies. It has only recently been translated into treating lung tumours. Goldberg et al.[10] inoculated VX2 sarcoma into rabbit lungs and performed RFA treatment following computed tomography (CT) guided placement of 19-gauge Turner needles. Histological analysis showed coagulative necrosis of the tumour and surrounding alveoli, with at least 95% of tumour nodules being necrotic in all treated cases. Miao et al.[11] again used RFA on the VX2 sarcoma tumours in rabbits and showed a 75% eradication rate following RFA treatment with a significant survival benefit in the animals treated as compared to control. Early clinical data were mainly in the form of 'ablate and resect' studies. Yang et al.[12] presented the results of a multicentre study in which 55% of their treated patients showed complete ablation. Nguyen et al.[13] reported a prospective study in which RFA was performed in early stage NSCLC at thoracotomy followed by resection. 38% of the patients showed complete ablation with 87.5% of the patients treated showing more than 80% non-viability of the tumour at histology.[13] Another study evaluated the efficacy of RFA, either under CT guidance or at thoracotomy, followed by surgical resection and showed complete ablation in 67% of the patients treated.[14] A systematic review of observational studies of RFA for Lung Cancer showed a median complete necrosis rate of 90% (range from 38 to 97%) with 1-, 2- and 3- year survival rates of 63–85%, 55–65% and 15–46% respectively.[15]

Patient selection and standard treatment protocol

Radiofrequency ablation is indicated in patients for whom treatment of Lung Cancer is expected to convey a survival benefit and/or improved quality of life.[16] RFA is usually reserved for patients with early stage I or II NSCLC, in whom a surgical resection is contraindicated. RFA can also be suitable in patients with advanced disease who responded to chemo/radio-therapies, but who have a persistent peripheral focus of disease.[17] RFA has also been used in isolated recurrence of NSCLC in post-surgical patient in whom further surgery is contra-indicated. Patients with limited peripheral lung metastases can also be suitable candidates for RFA treatment provided the primary cancer is controlled.[17] Exclusion criteria can usually be divided into tumour characteristics and patient factors. Large tumours (usually >5 cm), proximity to major pulmonary vessels or major bronchus, hilar tumours and more than three tumours in one lung are usually contraindicated for RFA treatment although absolute contra-indications tend to vary from institutions.[16–21] Patients with leukopenia, coagulation disorders, multi-organs impairment severe respiratory compromise or poor cardiac function are excluded from RFA treatment.[16–18,21]

Virtually all cases of RFA are carried out under CT guidance, even though there have been reports of US being used if the target lesion is in contact with the parietal pleura.[22] The procedure is usually carried out with local anaesthetics with conscious sedation and standard routine heart rate, oxygen saturation and blood pressure monitoring. Treatment time depends on the target lesion size, electrodes and generators used. The aim is to achieve complete ablation of the tumour along with a parenchymal margin of 0.5 cm[16,21] to 1 cm.[22] Following treatment, the needle track is usually ablated as well, to prevent rate cases of needle track seeding of tumour.[16,20–22] Post-procedure care usually involves repeat imaging of the chest to assess the presence of any pneumothorax and a 24 h observation period.

Evaluation of treatment response

Accurate imaging evaluation of RFA is challenging, because both a residual mass and an ablation zone are present, as compared to post-surgical or post-radiotherapy follow-up. RFA often induces an inflammatory reaction in the surrounding lung parenchyma, which may appear as ground glass opacification or even consolidation on imaging. Cavitation has also been reported post treatment.[23,24] These treatment specific changes seen on imaging tend to evolve over months to years which makes imaging interpretation challenging. Most centres use a 1-month follow-up CT scan as baseline, because the high-density treated area is usually larger than the initial tumour.[25] CT scans are repeated at 3 months, 6 months then every 6 months post procedure. Several factors are taken into account in assessing the treatment outcome. Tumour morphology, volume and contrast enhancement are usually followed over time.[16,18,20,26] Some centres use CT densitometry protocols, in which sequential images are taken post contrast injection, to increase sensitivity.[18] Positron emission tomography (PET) – CT has also been used to assess treatment response.[27,28] PET – CT provides the additional benefit of not being limited to anatomical evaluation only.[26] Diffusion-weighted Magnetic resonance imaging (MRI) is also being evaluated as a tool to identify incompletely treated tumours.[29] According to the Response Evaluation Criteria in Solid Tumours (RECIST), target tumours showing at least a 30% reduction in the longest diameter on CT scan, no evidence of tumour growth from the zone of ablation and no evidence of contrast enhancement were assumed to have responded completely.[30] However, the RECIST criteria do not account for the residual scar present post RFA treatment. To address this, a modified RECIST criteria (Table 1) has been described to take into account lesion size and quality but also metabolic activity on PET.[31]

Outcomes

As previously mentioned, the initial reported experience with RFA consisted mainly of observational studies. Zhu et al.[15] published a systematic literature review in 2008 which reported a 1-, 2- and 3-

Table 1
Modified RECIST criteria.[31]

Response	CT Mass size	CT mass quality	PET
Complete (Two of the following)	Lesion disappearance (scar) or less than 25% original size	Cyst cavity formation low density	SUV<2.5
Partial (one of the following)	More than 30% decrease in the sum LD of target lesions	Mass central necrosis or central cavity with liquid density	Decreased SUV or area of FDG uptake
Stable lesion (One of the following)	Less than 30% decrease in the sum LD of target lesions	Mass solid appearance, no central necrosis or cavity	Unchanged SUV or area of FDG uptake
Progression (Two of the following)	Increase of more than 20% in sum LD of target lesions	Solid mass, invasion adjacent structures	Higher SUV or larger area of FDG uptake

CT = computed tomography; FDG = fluorodeoxy glucose F18; LD = lesion diameter; PET = positron emission tomography, done selectively; RECIST = response evaluation criteria in solid tumors; SUV = standardized uptake value of fluorodeoxy glucose F18.

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