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Application of ablation techniques in the treatment of lung cancer - a review of recent reports

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ABSTRACT
Background: Lung cancer is the second most common and fatal cancer worldwide. The first-line treatment for early-stage primary lung cancer is surgical resection, but surgery is contraindicated in 60% of cases. Alternatives then include local treatments such as radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation. With the current scientific knowledge of these treatments, the fundamental question of their therapeutic efficacy must be answered.
Aim and methods: To present recent scientific findings on the efficacy of the three main methods of thermoablation for lung cancer. A systematic review of scientific papers on the indicated topics from the last 5 years was performed. Several dozen publications were selected for the purpose of this study.

Results: As shown in the studies, the therapeutic effect of MWA controls tumour progression with few side effects and high safety, especially in patients with tumours <3.5 cm in diameter. Cryotherapy, on the other hand, not only improves quality of life, but can also prolong patients' survival. The relatively low risk of this procedure goes hand in hand with its minimal invasiveness, leading to a low complication rate. RFA, on the other hand, shows no greater treatment efficacy than surgical resection, stereotactic radiotherapy.
Conclusions: MWA and cryoablation techniques are interesting alternatives to surgical resection for non-small cell lung cancer, improving the quality of life of patients regardless of the stage of their disease. The question of increasing the availability of this type of treatment in the health care system therefore remains crucial.
Keywords: MWA, RFA, cryoablation, NSCLC

INTRODUCTION

Lung cancer is the second most common and highest mortality cancer worldwide [1]. The first-line treatment for early-stage primary lung cancer is surgical resection. This is the preferred method, but in 60% of cases there are contraindications to surgery [2]. Alternatives then include local treatment methods such as image-guided thermal therapy (IGTA). This is a minimally invasive therapy that includes radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation and laser ablation [3]. The feasibility and safety of lung ablation, has been confirmed in the treatment of small lung cancer, especially lung tumours ≤3 cm, and is indicated in inoperable patients with early-stage primary lung cancer, as well as patients with oligo-metastasis or local recurrence. Thermoablative techniques are minimally invasive, show high rates of local control, shorter patient hospital stay, relatively lower cost and better patient tolerance compared to surgical resection [4]. In view of the above, it is imperative to keep an eye on the latest research findings to complement the information already gained on the efficacy of thermoablative techniques in the treatment of lung cancer.

AIMS AND METHODS

The aim of this study is to present recent scientific findings on the efficacy of the three main methods of thermoablation for lung cancer: microwave ablation (MWA), cryoablation and radiofrequency ablation (RFA). A systematic review from 2017 to 2022 was performed via Google Scholar. Thirty-six publications matching the topic of this review were selected.

RESULTS

Use of radiofrequency ablation (RFA) in the treatment of lung cancer

Radiofrequency ablation (RFA) is one method of thermal ablation performed under computed tomography (CT) guidance [5][6]. It was initially used as an alternative treatment for hepatocellular carcinoma (HCC) and later found application in the treatment of lung cancer and metastases. By increasing the temperature of the tumour tissue, it leads to degeneration and necrosis [6][7].

It is safe and effective in the treatment of lung cancer patients. In one meta-analysis, the technical success rate was 96%, the overall recurrence rate was 35%, the local tumour progression rate was 26%, the rate of major complications was 6% and the rate of benign complications was 27% [7].

RFA is an alternative to surgical treatment for early-stage non-small cell lung cancer (NSCLC) in patients who do not meet the criteria necessary for lung flap resection. Various studies have demonstrated the efficacy of RFA in destroying lung tissue - both healthy and tumour-lesioned. [6]

A meta-analysis comparing RFA with surgery showed no significant difference in 5-year overall survival (OS) rates in patients with early-stage NSCLC. [8]

In the treatment of inoperable early-stage NSCLC, the combination of external beam radiotherapy (EBRT) with RFA has been attempted, but due to the greater efficacy of stereotactic radiotherapy (SBRT), such treatment is not recommended. [9]

In a study comparing SBRT and RFA in the treatment of lung cancer, SBRT was shown to have a better local control rate (LC) and long-term overall survival (OS), while for short-term OS, both modalities had similar rates. [10]

Use of microwave ablation (MWA) in the treatment of lung cancer

MWA involves the placement of a microwave antenna in the tumour area through a percutaneous puncture. The advantages of MWA in the treatment of lung tumours compared with other IGTA techniques are faster ablation, larger ablation zones, less sensitivity of the tissue type to high temperatures and less impact of the 'heat sink' on perivascular tissues [11].

As studies show, the therapeutic effect of MWA in lung cancer is satisfactory, controlling tumour progression with few side effects and high safety. In one study, MWA was used in 113 patients with lung cancer, with tumour diameters ranging from 0.7- 6 cm. In all cases, vacuolisation, reduced density and reduction in tumour size or complete disappearance were observed. The local progression/recurrence rate was 15.9%. Importantly, the advanced stage group was more prone to local progression or recurrence, and tumours with larger diameters had a higher rate of local recurrence (5.7 per cent in early stage, 20.5 per cent in advanced stage, of which 81.3 per cent of local progression or recurrence occurred in patients with a tumour > 3 cm in diameter). The consecutive 3-year survival rate was 84.7 % in early-stage lung cancer patients and 71.7 % in advanced-stage patients. Complications were relatively rare and easily controlled. These were: in 27.4 % of cases, symptoms of post-ablation syndrome within the first three days after ablative treatment (including fever, weakness, nausea, vomiting), 10.6 % pneumothorax, 8 % pleural effusion, 9.7 % haemoptysis, 7.1 % pneumonia, 19.5 % pain during surgery, 5.3 % severe pain after surgery, and, importantly, no intra-operative or post-operative death occurred [12]. In comparison, in another study involving 15 inoperable stage I non-small cell lung cancer (NSCLC) patients receiving MWA, the local recurrence rate (LRR) was 31% with a median follow-up period of 12 months [11][13]. In a subsequent retrospective study, the LRR was 27.7% (median follow-up period 30 months) and overall survival (OS) rates at 1, 2, 3 and 5 years after MWA were 89%, 63%, 43% and 16%, respectively. The rate of local recurrence after MWA was approximately 25%-35%. Local recurrences occurred

in 23.1% of patients, with tumour diameter >3.5 cm being the only significant negative risk factor [11][14]. MWA has shown high efficacy and safety in the treatment of NSCLC patients with oligo-metastases. In one study, the treatment was successful in 91.1% of patients, with median PFS (progression-free survival) and OS of 14.0 and 47.8 months, respectively. 55.7% of patients developed complications and 29.6% developed serious complications. All complications resolved after appropriate treatment and there were no MWA-related deaths. Independent prognostic factors for PFS have also been established: female sex, metachronous disease, primary tumour surgery, total ablation, and factors for better OS: primary tumour surgery, female sex, synchronous disease, total ablation [15].
There are studies evaluating the efficacy of MWA in the treatment of patients with advanced NSCLC. In this setting, OS in patients with tumour size ≥4 cm was significantly lower compared to patients with smaller tumours. This is likely due to the more advanced stage of the disease and the lower likelihood of achieving complete tumour necrosis with MWA in the group with larger tumours. Importantly, the procedure can be safely repeated in cases of incomplete ablation or tumour progression. MWA can also be used effectively in large NSCLC in close proximity to anatomical structures [16].

In a study evaluating the technical safety, efficacy and complications of MWA therapy for lung tumours adjacent to interlobar fissures (within 5 mm of the interlobar fissure), the rate of complete ablation was 95.5 per cent, PFS rates at three, six, nine and 12 months were 89.4 per cent, 83.3 per cent, 74.2 per cent and 63.6 per cent, respectively, there were no ablation-related deaths and serious complications were observed in 18.2 per cent of cases [11]. In addition, MWA may have important applications in post-lung resection patients with tumour recurrence or metastasis. The results of the analyses show that MWA is effective and improves survival for peripheral lung malignancies in patients after pneumonectomy. In this study, the technical success rate of a single session was 100%, the percentage of complete ablation was 90.9%. The median overall survival was 20 months, and the 1-, 2- and 3-year overall survival rates were 88.7%, 63.6% and 42.3%, respectively [17].
There are studies that show positive effects of combining MWA therapy with chemotherapy in the treatment of lung cancer. One such study suggests that MWA in combination with chemotherapy may provide better survival compared to chemotherapy alone in patients with advanced non-small cell lung cancer. Median PFS was 10.3 months in the MWA plus chemotherapy group and 4.9 months in the chemotherapy alone group.

Disease progression was observed in 54% of patients in the MWA plus chemotherapy group and 63% of patients in the chemotherapy alone group. Death was observed in 32% of patients in the MWA plus chemotherapy group and 66% in the chemotherapy alone group. Longer OS was observed in the MWA plus chemotherapy group compared to the chemotherapy group.
Complications associated with MWA were common but amenable to effective treatment [18]. A similar use of MWA has been found in the treatment of advanced NSCLC with epidermal growth factor receptor (EGFR) mutation with extracranial metastasis. Treatment with consolidation therapy with MWA significantly improved PFS and OS compared with the monotherapy group. The results of this study suggest that MWA as a local consolidation therapy after first-line treatment, leads to better disease control and survival than monotherapy [19].

Porównanie MWA do RFA

There have also been numerous studies comparing MWA to other lung cancer treatments. One study comparing the two modalities found results indicating longer survival with RFA compared to MWA and better survival in patients with lung metastases after RFA [20]. A similar study comparing these methods (the LUMIRA study) showed an advantage of MWA over RFA in terms of less intraoperative pain and a significant reduction in tumour mass [21].

Use of cryoablation in the treatment of lung cancer

Cryoablation consists of two phases: freezing and thawing, which should be repeated a few times. The whole process is depicted using computed tomography and by Joule-Thomson effect (describing the isenthalpic throttling theory of gases), the area of „ice ball" is formed [22, 23]. Two the most commonly used gases to this procedure are argon and helium [24]. Using ablative techniques together with immunotherapy or chemotherapy was analysed – combination of cryoablation with nivolumab was found to be more effective than cryoablation itself in terms of immune function and short-term efficacy [25]. Cryoablation supports drug penetration through increasing the permeability of blood vessels.
Chemotherapy leads to the reduction of tumour volume and it is possible by immune enhancement caused by ablation techniques [26].
Mechanism that lies under this process is based on direct and indirect effects of cold. During the freezing phase (−196°C), formation of extracellular crystals is observed, which causes water migration and dehydration of the cell itself. Other effects are: decreased metabolism, protein denaturation and mechanical damage of cell

membranes, which causes cell death and apoptosis due to the activation of caspase 3 and the bac protein [23] [24] [27]. Freezing should take at least 10 minutes, because the temperature should migrate to the periphery zone, which should be exceeded at least 5-8mm to let the temperature reach the entire lesion [28]. Then, using temperature up to 80°C in the process of thawing, a reverse effect is observed – water coming back to the cell causes its membrane disruption [27]. High temperature is beneficial to the blood supply system – it prevents bleeding. Another profitable effect is the collapse of the blood supply – tissue ischemia is present by the damage of vessels walls due to the ice formation in the endothelium. Microvascular thrombosis and local edema contribute to changes in the tumour's environment. Cryoablation should be multiplied to be able to reach larger zones and provide effective cytotoxicity in a shorter period of time [27]. The second freezing cycle should include decreased temperature [23].

Using cryoablation is especially needed in patients, who can not undergo surgery – which is nearly 80% of all diagnosed patients with occurence of lung cancer [29]. Nowadays cryoablation is recommended as an alternative to resection in the treatment of medically operable non-small cell lung cancer (NSCLC) according to National Comprehensive Cancer Network [26]. During past years, ablation techniques were utilised mostly in the treatment of early stage inoperable lung cancers, but more and more research shows that this treatment might be beneficial for other stages as well. Access to certain lesions might be limited due to the physical location of the tumour that can not be reached by percutaneous puncture. Usage of bronchoscopy cryoablation is necessary in those cases, which was already reported ex vivo [30]. Lesions adjacent to the mediastinum and tracheobronchial area may be also treated using ablation techniques [27].

Awareness of possible advantages of implementing ablative therapies in everyday work is crucial. Not only does cryotherapy improve quality of life, but also can prolong patients' survival. Relatively low risk of this procedure goes along with being minimally invasive, which leads to low rate of complications (many of them being self-limiting) and low mortality rates [31]. Median overall survival after treatment equals more than 5 years. The one-year survival rate of almost 82% and progression-free rate of 27.8% were observed in patients after failure of chemoradiotherapy [22][32].

Even though ablation techniques are minimally invasive, they may cause complications such as: pneumothorax, phrenic nerve injury, pulmonary haemorrhage, ablation-zone infections, pulmonary embolisms, pleural effusion, haemoptysis, tumour implantation, bronchocutaneous or bronchopleural fistula formation. The serious ones are rare, but may be life-threatening – for instance pulmonary embolism [29][33]. To reduce the incidence and grade of haemoptysis and delay its onset over the immediate recovery period – using active thaw at the end of the cryoablation procedure is recommended [34].

During COVID-19 pandemic the access to interventional oncology treatment was limited due to the shortage of anesthesiologic resources, qualified specialists and access to hospital beds. A challenge was to find a suitable therapy, which can be delivered with a minimal sedation – a perfect solution was implementing a thermal ablation as a key anti-tumour procedure [35]. Postponing oncological treatment was present in patients infected by SARS-CoV-2. The National Health Service (NHS) recommended avoidance of thermal ablation in oncological patients older than 60 years old with primary lung cancer with pre existing respiratory or cardiovascular comorbidities [36][37].

CONCLUSIONS

From the information presented above, MWA and cryoablation are effective alternatives to surgical resection for patients with non-small cell lung cancer [12]. MWA controls tumour progression with few side effects and high safety, especially in patients with tumours <3.5 cm in diameter [11][14]. MWA also shows high efficacy and safety in the treatment of NSCLC patients with oligo-metastases, after local recurrence and in cases of tumours located in hard-to-reach locations such as lung interlobular fissures [15][16][17]. RFA, on the other hand, does not show greater treatment efficacy than surgical resection, stereotactic radiotherapy, and there are different results of studies comparing it to MWA [8][9][20][21].

In contrast, cryoablation is recommended as an alternative to resection for the treatment of medically operable non-small cell lung cancer (NSCLC) according to the National Comprehensive Cancer Network [26]. Due to the low need for anaesthetics during procedures, cryoablation proved to be an excellent alternative during the COVID-19 pandemic, as it allowed hospitals to maintain continuity of procedures performed when sedation was required for SARS CoV-2-infected patients [35]. In conclusion, the therapeutic approaches presented represent an interesting alternative to the commonly used surgical resection for the treatment of NSCLC. It is therefore necessary to increase the availability of this therapeutic method in the offer of health care systems, and this availability, using Poland as an example, is not satisfactory (only in June 2022, the first cryoablation procedure for lung cancer was performed in the country) which must be improved immediately [38].

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