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Primary and metastatic malignancies of the lung: Retrospective analysis of the CT-guided high-dose rate brachytherapy (CT-HDRBT) ablation in tumours < 4 cm and ≥ 4 cm

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ABSTRACT

Background: Minimal invasive local therapies are alternative treatment options in patients with primary and metastatic lung malignancies being not eligible for resection. However, thermal ablations are often limited by large tumour volumes.

Purpose: To evaluate the efficacy and safety of CT-HDRBT in pulmonary tumours ≥ 4 cm compared to smaller tumours.

Material and methods: In this retrospective study, 74 consecutive patients (mean age: 63 ± 12; m: 39, w: 35) with a total of 175 tumours treated in 132 interventions were enrolled between October 2003 and September 2016. Primary and assisted local tumour control (LTC), progression free survival (PFS) and overall survival (OS) after first CT-HDBRT were identified for two subgroups with tumours < 4 cm (A) as well as ≥ 4 cm (B) using the Kaplan-Meier-Method. Radiation parameters and side effects were recorded. Log-Rank-Test and Mann-Whitney-U-Test were performed for statistical analyses with p-values < 0.05 considered as significant.

Results: There was no statistical difference in coverage with prescribed radiation dose (A:19.78 ± 8.62 mm (range 5–39 mm), 99.56 ± 0.99%; B:61.70 ± 21.09 mm (41–100 mm), 94.81 ± 7.19%, p = 0.263). LTC rates after 0.5-,1-,2-,3- and 5-years were higher in A compared to B (A:85%/74%/63%/60%/46%, B:71%/37%/32%/32%/32%) with longer primary (A:11months, B:5months, p = 0.003) and assisted LTC (A:9months B:20months, p = 0.339). Longer OS was observed in A (A:18.5months, B:14.5months, p = 0.011) with longer OS rates (A:96%/87%/60%/48%/19%, B:92%/73%/20%/20%/0%). Complication assessment revealed no bleedings, 16.6% pneumothoraxes and 48.5% of mild radiation fibrosis without clinical symptoms.

Conclusion: In conclusion, higher LTC and OS were observed in patients with primary lung malignancies < 4 cm. Nevertheless, CT-HDRBT is a safe and feasible alternative even in larger tumours ≥ 4 cm.

1. Introduction

Surgical resection remains the standard treatment in early stage primary lung cancer and in pulmonary metastatic disease, if not excluded by locally advanced disease with multiple intra- and extrapulmonary metastases, restricted cardiopulmonary function or limiting additional comorbidities [1–6]. Alternatively, stereotactic body radiotherapy (SBRT) and local ablation are efficient treatment options in patients not eligible for surgery [3,7,8]. In advanced cases with multiple metastases, systemic chemotherapy is the standard treatment [3,9].

There are different approaches of local ablation such as radiofrequency (RFA), microwave ablation (MWA) and less common cryoablation as well as laser induced thermotherapy (LITT). However, radiofrequency ablation is currently the most frequently used ablation technique in lung tumours [8]. Thermal coagulation is induced by

Abbreviations: CT-HDRBT, CT-guided high dose rate brachytherapy; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; MWA, microwave ablation; LITT, laser induced thermotherapy; CTx, chemotherapy; RTx, radiation therapy; pLTC, primary local tumour control; aLTC, assisted local tumour control; PFS, progression free survival; TTPP, time to pulmonary progression; OS, overall survival; CTV, clinical target volume; aPTT, activated partial thromboplastin time

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applicators with rapidly changing electromagnetic fields with frequencies less than 30 MHz. The technique was first described in animal models in 1995 [10] and in patients in 2002 [11]. RFA zones up to 5 cm in diameter are achievable [12,13]. However, safety margins depending on the tumour entity vary from 6 to 8 mm limiting the technique to tumours of approximately 3 cm in diameter [14]. Furthermore, RFA is prone to heat sink effects caused by blood flow and air exchange [15,16]. Microwave ablation uses frequencies ranging from 300 MHz up to 300 GHz using dielectric hysteresis, so that energy is not distributed by electric currents resulting in higher ablative temperatures and shorter treatments as well as in larger ablations zones [17,18].

CT-guided high dose rate brachytherapy (CT-HDRBT) is an evolving and promising local ablative treatment option inducing cell damage through a single fraction high dose radiation with an iridium-192 source in afterloading technique. As other local therapies such as RFA and MWA, CT-HDRBT proved in several studies its effectiveness and safety in various indications such as primary and secondary liver cancer or lymph node metastases and even in tumours larger than 5 cm in diameter [19,20]. So far, few clinical studies examined the use of CT-HDRBT to treat primary and metastatic lung malignancies. These studies were limited by small patient numbers and only two studies reported survival data as long as two years [21–24].

The purpose of this study was to evaluate the efficacy and safety of CT-HDRBT in primary and metastatic lung malignancies ≥4 cm in diameter compared to smaller tumours.

2. Material and methods

74 consecutive patients with a total of 175 tumours treated with CT-HDRBT for primary or metastatic lung malignancies were enrolled in this retrospective, single center study (mean age: 63 ± 12; m: 39, w: 35, Table 1) between October 2003 and September 2016. A minority of patients were previously being studied and published under different aims with shorter follow-up periods. Patients were referred by oncologists and surgeons for therapy. All indications were approved by our interdisciplinary tumour board. Institutional ethics committee approval and written informed consent were obtained.

Brachytherapy was contraindicated in patients with impaired coagulation (platelets < 50,000/μL, prothrombin time < 50%, aPTT > 50 s) and multifocal tumour growth (N > 5), unless segmental bronchial obstruction was anticipated. In cases of bipulmonary disease only one side was treated per session.

2.1. Procedure

Depending on previous imaging, unenhanced computed tomography was performed in prone or supine position to confirm feasibility and to assess tumour extension right before therapy at our interventional CT scanner. Once the target tumour was identified, skin disinfection and sterile dressing was applied. All patients were treated under mild intravenous analgosedation using fentanyl and midazolam. Moreover, local anesthesia with lidocaine ensured patient's comfort. During the whole procedure, electrocardiography, blood pressure and oxygen saturation measurements were performed. In addition, all patients received 2 l/min through a nasal oxygen tube.

Table 1
Treated entities.

Entity	Number of Patients (< 4 cm / ≥4 cm)
Colorectal Cancer	23 (17 / 6)
Sarcoma	16 (6 / 10)
Primary Lung Cancer	10 (5 / 5)
Renal Cancer	4 (4 / 0)
Biliary Tract Carcinoma	3 (3 / 0)
Breast Cancer	2 (2 / 0)
Esophageal cancer	2 (2 / 0)
Pancreatic carcinoma	2 (2 / 0)
Adenoid cystic cancer	2 (1 / 1)
Parotic gland tumour	2 (1 / 1)
Squamous cell cancer	2 (1 / 1)
Chronic lymphatic lymphoma	1 (1 / 0)
Gastric cancer	1 (1 / 0)
Ovarian cancer	1 (1 / 0)
Uveal melanoma	1 (1 / 0)
Hepatocellular carcinoma	1 (0 / 1)
Urothelial carcinoma	1 (0 / 1)

The target tumour was punctured with a 17 G needle using CT-fluoroscopy for guidance. Afterwards, a 6 F sheath [CORDIS, Cardinal Health, AVANTI+, 6 F, 23 cm length, Miami Lakes, FL, USA] was advanced over a 0.035″ guide wire [Amplatz Super Stiff, Boston Scientific, Natick, MA, USA] in Seldinger technique followed by the positioning of a 6 F afterloading catheter [Primed, Halberstadt, Germany] through the sheath into the target tumour. A final CT-scan of the entire thorax ensured correct catheter placement and the detection of early side effects such as pneumothorax, active haemorrhage and pleural effusions.

Next, 3D radiation planning [Brachyvision, Varian Medical Systems, Palo Alto, CA, USA] using the post-interventional CT images was performed registering the catheters, the clinical target volume (CTV) and potential risk structures. CTV was defined as tumour tissue intended for radiation (Fig. 1). Calculation of the brachytherapy plan included dwell times and locations of the iridium-192 source [Gammamed, Varian Medical Systems, Palo Alto, CA, USA]. The planned target dose enclosing the tumour was at least 20 Gy resulting in considerably higher doses in the tumour centre and around the brachytherapy catheters. If necessary, the target dose was reduced in intention to protect adjacent risk structures (Table 2). As soon as the brachytherapy was finished, catheters and sheaths were extracted while applying fibrin glue along the puncture site (Tisseel, Baxter, Deerfield, IL; USA) through a dilator placed through the sheath.

2.2. Follow up

Early post-interventional sides effects such as pneumothorax were ruled out performing a chest x-ray examination after 4 h and on the following day if necessary. Moreover, clinical visits and CT follow-up were performed at 8 weeks and 5 months after therapy. Afterwards chest CT was performed every 6th month. If possible, additional CT-HDRBT was offered in cases of tumour progression.

2.3. Parameters

Tumour outcome was evaluated by the median duration of local tumour control (LTC), progression free survival (PFS) and overall survival (OS). Furthermore, the local tumour control rate (LTC rate), progression free survival (PFS rate) and overall survival rates (OS rates) were calculated for progression free survival (PFS) and overall survival (OS). Furthermore, the local tumour control rate (LTC rate), progression free survival (PFS rate) and overall survival rates (OS rates) were calculated for 0.5-, 1-, 2-, 3- and 5-years after first CT-HDRBT.

Primary LTC (pLTC) was calculated from the date of CT-HDRBT to the date of progress of a treated tumour. Assisted LTC (aLTC) was defined as local tumour control allowing further CT-HDRBT in case of a local recurrence. TTPP describes the time to pulmonary progression after first brachytherapy. PFS was defined as interval between the date of first tumour ablation to any tumour progress. OS described the period from first CT-HDRBT to the date of death or last date of follow up.

2.4. Analysis and Statistics

Descriptive statistics were used to analyse the frequency of additional therapies, side effects such as active bleeding, pneumothorax, intervention associated pleural effusion as well as perifocal fibrosis and

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