CT-Guided Interstitial Brachytherapy of Primary and Secondary Lung Malignancies

Results of a Prospective Phase II Trial

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Background and Purpose: CT-guided interstitial brachytherapy of primary lung malignancies and pulmonary metastases represents a novel interventional technique, combining conventional high-dose-rate (HDR) iridium-192 (^{192}Ir) brachytherapy with modern CT guidance for applicator positioning and computer-aided 3-D radiation treatment planning. The purpose of this study was to assess safety and efficacy of this technique.
Patients and Methods: 30 patients with 83 primary or secondary lung malignancies were recruited in a prospective nonrandomized trial (Table 1). After catheter positioning under CT fluoroscopy, a spiral CT was acquired for treatment planning (Figure 1). All but two patients received a defined single dose (coverage > 99%) of at least 20 Gy from a ^{192}Ir source in HDR technique.
Results: Adverse effects were nausea (n = 3, 6%), minor (n = 6, 12%) and one major pneumothorax (2%). Post intervention, no changes of vital capacity and forced expiratory volume could be detected. The median follow-up period was 9 months (1–21 months) with a local tumor control of 91% at 12 months (Figure 2).
Conclusion: CT-guided interstitial brachytherapy proved to be safe and effective for the treatment of primary and secondary lung malignancies.

Key Words: Brachytherapy · Lung cancer · Pulmonary metastases · CT · Intervention · NSCLC

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CT-gesteuerte interstitielle Brachytherapie von NSCLC und pulmonalen Metastasen. Ergebnisse einer prospektiven Phase-II-Studie

Hintergrund und Ziel: Die CT-gesteuerte interstitielle Brachytherapie von primären Lungenmalignomen und Lungenmetastasen stellt eine weiterentwickelte interventionelle Technik dar, welche die konventionelle Hochdosisraten-(HDR)-Iridium-192-(^{192}Ir-)Brachytherapie mittels moderner CT-Bildführung zur Applikatorpositionierung und computergestützter 3-D-Bestrahlungsplanung kombiniert. Ziel der Studie war die Analyse von Sicherheit und Effektivität dieses Verfahrens.
Patienten und Methodik: 30 Patienten mit 83 primären Lungenmalignomen oder pulmonalen Metastasen wurden in einer prospektiven, nicht randomisierten Phase-II-Studie behandelt (Tabelle 1). Nach Katheterpositionierung unter CT-Fluoroskopie erfolgte die Gewinnung eines 3-D-Datensatzes für die Bestrahlungsplanung (Abbildung 1). Alle Patienten bis auf zwei erhielten eine vorgeschriebene Einzeldosis (Abdeckung > 99%) von mindestens 20 Gy über eine ^{192}Ir-Quelle in HDR-Technik.
Ergebnisse: Minorkomplikationen waren Übelkeit (n = 3, 6%), diskreter (n = 6, 12%) sowie ein therapiebedürftiger Pneumothorax (2%). Postinterventionell ergaben sich keine Änderungen der Vitalkapazität oder des forcierten exspiratorischen Volumens. Die mediane Nachbeobachtungszeit betrug 9 Monate (1–21 Monate). Die lokale Tumorkontrolle lag nach 12 Monaten bei 91% (Abbildung 2).
Schlussfolgerung: Die CT-gesteuerte interstitielle HDR-Brachytherapie stellt ein sicheres und effektives Verfahren zur Behandlung von primären Lungenmalignomen und pulmonalen Metastasen dar.

Schlüsselwörter: Brachytherapie · CT · Intervention · NSCLC · Lungenmetastase · Bronchialkarzinom

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Introduction

Resection is generally recognized as the initial therapy measure for solitary pulmonary metastases as well as localized primary lung tumors and has shown clear evidence to improve prognosis in these patients [5, 9]. Resection of primary lung malignancies with a curative intention is only feasible in < 30% of all patients. Individuals with multiple lung metastases or further manifestations are rarely candidates for invasive surgical procedures due to a critical benefit/risk consideration.

In the context of multimodal oncologic therapy concepts a minimally invasive approach is often desired. So far, for the interventional ablation of lung malignancies mostly hyperthermic therapy approaches were available, whereof radiofrequency ablation (RFA) and laser-induced thermotherapy (LITT) in particular found clinical application [11, 13, 25]. Similarities to these procedures refer to catheter application, differences exist regarding the kind and reliability of the energy distribution. Hyperthermal ablation procedures are characterized by high thermal energy deposition into the target volume, which by temperatures > 50 °C leads to coagulation of the tissue. As a matter of principle limitations exist regarding the size of the target volume of < 5 cm for LITT and RFA and the localization of the target volume, caused by cooling effects due to tumor perfusion and neighboring vessels. In addition, the instantaneous thermal effect holds, at least theoretically, a higher risk of acute complications and, by formation of necrotic cavities, a higher risk of late adverse effects [11, 27].

CT-guided brachytherapy was initially applied in the treatment of liver malignancies [21, 22]. With this novel technique, highly effective radiation doses are applied as a single fraction, ensuring protracted cell killing over a period of up to several weeks or months. Compared to other interventional procedures, advantages exist regarding interference-free and accurately predictable energy distribution, treatable size of a target lesion and lower rate of acute adverse effects possible by maintaining tissue continuity [15]. Extensive experiences with this technique had been collected during several preceding studies targeting liver malignancies as well as one study targeting lung malignancies [23]. Recently, non-small cell lung cancer (NSCLC) and other malignancies have been targeted by image-guided brachytherapy in studies by other groups [8, 12, 14, 16, 18].

The aim of the study reported herein was to evaluate the safety and efficacy of high-dose-rate (HDR) CT-guided interstitial brachytherapy in the treatment of primary lung malignancies and pulmonary metastases.

Patients and Methods

Study Design

Between January 2003 and September 2005, 30 consecutive patients with 83 singular pulmonary lesions were included in this prospective, nonrandomized phase II trial. Both, patients with pulmonary metastases of colorectal carcinomas or metastases of other tumor entities as well as patients with primary NSCLC were included into the trial. The study was approved by the local ethics committee. Written informed consent was obtained from all patients before entry into this study.

Study Endpoints

Primary endpoints of the study were adverse events and local tumor control.

Inclusion Criteria

We included patients with one or more primary or secondary lung malignancies, a Karnofsky Index of ≥ 75% as well as appropriate coagulation parameters (thrombocytes > 100,000/nl, Quick > 50%, partial thromboplastin time < 50 s). The administration of anticoagulants like coumarin derivatives and inhibitors of platelet aggregation were discontinued 7 days prior to intervention. All patients displayed contraindications to surgery or had rejected surgical treatment.

Patient Population

The patient population comprised 30 consecutive patients, 14 male and 16 female, with 83 primary or secondary pulmonary malignancies. Both, patients with NSCLC (n = 6, 20%) as well as patients with pulmonary metastases of colorectal carcinomas (n = 13, 43%) or metastases of other tumor entities (n = 11, 37%) were treated (Table 1). Among these were breast cancer (n = 4, 13%), hypernephroid renal carcinomas (n = 3, 10%), soft-tissue sarcomas (n = 3, 10%), and laryngeal cancer (n = 1, 3%). Median age was 61 years (33–79 years). Two patients had a history of previous lung surgery of the respective side and demonstrated a diminished forced expiratory volume (FEV_1) and vital capacity (VC). With these patients a pre- and postinterventional determination of FEV_1 and VC was obtained.

Interventional Procedure

Positioning of brachytherapy applicators was performed employing a fluoroscopy CT (Somatom™ Plus 4, Siemens, Erlan-

Table 1. Patient characteristics. NSCLC: non-small cell lung cancer.

Tabelle 1. Patientencharakteristika. NSCLC: nichtkleinzelliges Lungenkarzinom.

Tumor entity	Patients (n)	Patients with singular lesions (n)	Treated lesions (n)	Interventions (n)
Colorectal carcinoma	13	5	35	21
Primary NSCLC	4	4	4	4
Metastases of NSCLC	2	0	4	4
Breast cancer	4	2	8	6
Soft-tissue sarcoma	3	1	10	7
Hypernephroid renal carcinoma	3	2	21	7
Laryngeal cancer	1	1	1	1

gen, Germany). Generally, for a lesion ≤ 4 cm in diameter one catheter was used. Depending on size and configuration also multiple catheters were required for individual lesions. After puncture with an 18-G needle, an angiography sheath of 6 F (Radiofocus™, Terumo, Tokyo, Japan) was inserted over a stiff angiography guide wire (Amplatz™, Boston Scientific, Natick, MA, USA). Following removal of the guide wire a 16-G brachytherapy catheter (Cook, Bjaeverskov, Denmark) was placed in the sheath. Directly after catheter application a CT of the lung was acquired in a single breathhold for irradiation planning.

All interventions were performed under i.v. analgosedation. Initial doses of 50 µg fentanyl und 1 mg midazolam were applied, with increased doses according to the individual discomfort level of each patient. Less than 1 ml of fibrin tissue adhesive (Tissucol™, Baxter, Unterschleißheim, Germany) was injected through the brachytherapy sheath into the lung periphery during catheter removal.

All interventions were performed on an inpatient basis at our radiooncology/interventional ward with a usual stay of 4 full days.

Irradiation and Radiation Treatment Planning

Computer-aided 3-D radiation treatment planning using the acquired 3-D dataset was performed using Brachyvision™ software (Gammamed™, Varian, Palo Alto, CA, USA; Figure 1). First, all brachytherapy catheters were digitized from their tip to the exit point. Then, clinical target volume (CTV) and risk structures were delineated. For each pulmonary lesion an individual target volume was defined. One or multiple placed catheters contributed variably to a single target volume. Source dwell points and times were optimized manually, afterwards verified graphically and by dose-volume histogram (DVH) employing the planning software to generate a complete coverage of the target volume. We prescribed a minimal dose of 20 Gy covering the CTV. Dose maximums of > 50 Gy in central tumor areas were admitted without restriction. One up to six lesions were treated during one session, in which only unilateral treatment was performed to avoid the risk of a bilateral pneumothorax. All irradiations were performed as a single-fraction irradiation using an afterloading system (Gammamed™, Varian). Iridium-192 (^{192}Ir) with a nominal activity of 10 Ci and a diameter of < 1 mm was used as a radiation source.

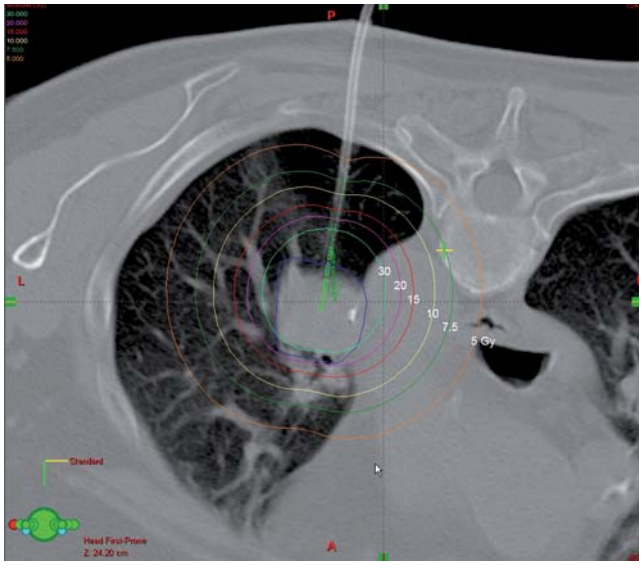

Figure 1. Radiation treatment planning after application of the brachytherapy catheter. Note the steep gradient with the inner isodose illustrating a dose of 30 Gy, the outer isodose of 5 Gy. The depicted myelon receives a total dose of approximately 2 Gy.

Abbildung 1. Bestrahlungsplanung nach Applikation des Brachytherapiekatheters. Man beachte den steilen Dosisabfall im umliegenden Gewebe. Die innere Isodosenlinie entspricht 30 Gy, die äußere 5 Gy. Das abgebildete Myelon wird einer Gesamtdosis von etwa 2 Gy exponiert.

Follow-up

On day 1 and 3 post intervention, a clinical examination was performed including hematologic and biochemical laboratory analyses. The intended follow-up period was 2 years, with visits 6 and 12 weeks post intervention, then every 12 weeks repeatedly for clinical examination, blood sampling, and CT examination of the thorax.

Definition of Remission Criteria and Local Control Rates

Local tumor control after brachytherapy was defined according to modified WHO response criteria for solid tumors and represents either stable disease (SD), partial (PR) or complete remission (CR) of the treated lesion. Any increase > 20% in diameter of a singular lesion was interpreted as progression.

Statistical Analysis

Statistical analysis was performed employing the Kaplan-Meier method.

Results

30 patients with 83 singular lesions were treated in 50 therapy sessions. One to six (median two) lesions were treated during each session. 50 out of 51 interventions were technically successful. One intervention was terminated due to a displacement of an angiography sheath.

A complete coverage (> 99%) of the tumor with the prescribed dose of 20 Gy could be accomplished in 81 lesions. In two lesions the dose was reduced to 15 Gy to spare adjacent risk structures. The mean tumor diameter was 2.5 cm (0.6–11 cm). In 79 lesions only one central applicator was used, two lesions of 5.5 and 6.5 cm were treated with two applicators each. For two very large lesions nine and ten catheters were used, respectively. In two sessions one catheter was used for two lesions simultaneously. Total irradiation time typically ranged between 3 and 15 min.

Minor complications included nausea (n = 3, 6%) and discrete pneumothorax (n = 6, 12%) which were treated conservatively and showed complete regression after 24 h. One major pneumothorax (n = 1, 2%) was treated with a 12-F chest tube and constant suction for 24 h.

Two patients had a history of previous lung surgery of the respective side, a total of six patients demonstrated a diminished lung function before brachytherapy with a VC of < 85% (minimum 40%; n = 6, 20%) and an FEV_1/VC of < 70% (minimum 17%; n = 6, 20%), respectively. No significant changes of VC or FEV_1 were noted during follow-up.

According to modified WHO criteria 0 (0%), 24 (36%), and 42 (64%) of 66 treated lesions exhibited CR, PR, and SD, respectively, after 3 months. Response rate, defined as the sum of CR and PR was calculated at 36%, although actual clinical progression was only found in four of the treated lesions later in follow-up. Thereof three treated lesions showed local tumor recurrence at 5, 5, and 14 months after treatment. Both lesions which showed progression at 5 months occurred in one patient with pulmonary metastases of colorectal carcinoma, suggesting a radiation-insensitive tumor clone. The latest reoccurrence at 14 months developed in a patient with soft-tissue sarcoma. One lung abscess occurred in combination with local tumor progression 9 months post intervention in a patient with laryngeal cancer.

Median follow-up period was 9 months (1–21 months) with a local tumor control of 91% after 12 months in the Kaplan-Meier analysis (Figure 2).

Discussion

With computer-aided 3-D radiation treatment planning on the basis of interventionally placed brachytherapy catheters, the optimum dose distribution relative to the target volume can be computed before application of the ^{192}Ir source (Figure 1). With adequate catheter positioning, both technical success (e.g., complete coverage of the target volume with 20 Gy) as well as protection of risk structures can be accomplished. Dose distribution is computed within the treatment planning system and can be delivered with a precision of > 95%. By contrast, with thermal ablation procedures, the deposited thermal dose inside the target volume cannot be determined as precisely as in irradiation, since it is influenced by several parameters such as tissue inhomogeneity, perfusion, thermal conductivity/capacity, and, finally, is significantly dependent on tissue alterations during ablation (e.g., change of impedance, carbonization). The phenomenon of perfusion-mediated tissue cooling which limits temperature elevation and possibly sufficient ablation in overly perfused tumor areas and localizations adjacent to large vessels does not exist in brachytherapy as a matter of principle. Thus, clear advantages in favor of brachytherapy exist with respect to conformity and control of dose distribution, which becomes especially important with adjacent risk structures.

Due to firm applicator fixation inside the lesion, displacement of the applicator relative to the tumor is unlikely. This applies to brachytherapy as well as to LITT and RFA. By contrast, displacement of pulmonary tumors due to breathing motion reduces accuracy in conventional and stereotactic percutaneous irradiation [10]. Hereby, both gating (linear accelerators) and tracking techniques (Cyberknife™, Accuray, Sunnyvale, CA, USA), as well as abdominal compression (to reduce breathing motion) are used, though none of these techniques is currently clinical routine [7]. Displacement of lesions by breathing can be reduced to 1 cm, with significant individual differences [10, 17, 26]. In conventional radiation therapy specification of target volumes must consider breathing motion by means of a larger safety margin to accomplish an effective dose in the target volume, resulting in considerably higher volume exposure of the surrounding tissue. Since the pulmonary tolerance dose decreases with increased irradiated volumes [6], conventional irradiation of larger volumes can lead to restricted applicable tumor doses.

From a physical point of view the energy deposition by an implanted irradiation source represents the best method to irradiate small target volumes with high doses [1, 4, 28]. Hereby, areas of excessive doses of > 50 Gy in the center of the target volume can be accepted. This might represent an additional safety factor for complete ablation in central hypoxic areas of the tumor [2–4, 19, 20, 24, 28] and could be an additional reason for the impressive local control rate, comparable to first results of other groups [12]. Additionally, due to the steep dose gradient, adjacent structures can easily be spared, which is especially important in central pulmonary localizations.

The size of a lesion can be a limiting factor in interventional ablative procedures. With brachytherapy, larger target volumes can be treated either by increase of irradiation time

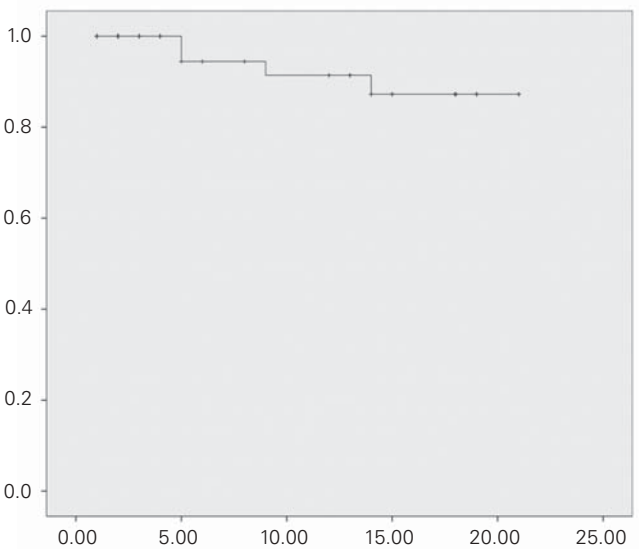

Figure 2. Local tumor control after CT-guided brachytherapy (Kaplan-Meier curve plotting).

Abbildung 2. Lokale Tumorkontrolle durch CT-gesteuerte Brachytherapie (nach Kaplan-Meier).

or by implantation of multiple catheters, if higher inhomogeneity of the radiation dose can be accepted.

HDR brachytherapy is characterized by high dose deposition into the target volume. This radiation dose, however, does not lead to instantaneous necrosis or breakdown of tissue structure with acute formation of cavities. Cytotoxic effects begin shortly after irradiation and can be expressed over the course of weeks and months, whereby structural changes correspond to slow reorganization rather than instantaneous structural damage which is characteristic of thermal procedures [15]. This might be a cause for the considerably higher rate of acute complications like pneumothoraces in 30–50% of the treatments employing thermoablative procedures, as well as for the formation of cavities, filled with air and necrotic tissue [11, 13, 25]. Compared to RFA with minor pneumothorax in 35% of the interventions [27] and major pneumothorax (necessitating a chest tube) in 7%, considerably lower rates of 12% (minor) and 2% (major pneumothorax) were found with brachytherapy. Another reason might be the application of fibrin adhesive into the sheath simultaneously during retraction. This measure was restricted to 2 cm of the lung periphery to avoid the risk of embolism. Despite missing proof, positive results allow us to continue the use of tissue fibrin adhesive.

Hemoptysis, seen in 11% after RFA, and pleural effusions were not encountered following brachytherapy.

In follow-up, most of the treated lesions exhibited only minor changes in configuration and overall volume. Excepting four tumor reoccurrences, these lesions exhibited no signs of progression during follow-up. Apparently, in HDR interstitial brachytherapy of the lung, generally accepted response criteria cannot fully describe the actual clinical response, demonstrated by absence of clinical signs of progression in follow-up. One explanation for the lack of CR is the formation of focal radiation fibrosis, even though this was not confirmed by pathologic examination. Response rates, defined as the sum of PR and CR, will appear paradoxically low, so in the context of evaluating effectiveness of the method local tumor control seems to be an appropriate parameter.

At present, our group is preparing and performing several trials from phase I–III employing CT- and MRI-guided interstitial brachytherapy and other interventional oncologic approaches, targeting a wide range of primary tumor entities and metastases in thoracic, abdominal and pelvic locations. After promising results, we will further evaluate interventional brachytherapy as an additional tool in multimodal oncologic therapy concepts. Furthermore, we will investigate the effectivity of the method compared to conventional therapy concepts.

Conclusion

CT-guided interstitial brachytherapy proved to be safe and effective for the therapy of primary lung carcinomas and pulmonary metastases. Because of its precise conformality to a plan and its predictable energy deposition, malignancies with problematic localizations, which cannot be reached by surgery or thermal ablation procedures, can be treated safely and effectively. Our data show promising local control rates, and nevertheless fewer complications compared to other interventional ablation procedures. Based on our positive experiences, we are going to apply this technique on an outpatient basis in the near future.

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