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ORIGINAL ARTICLE

Lung tumor tracking during stereotactic radiotherapy treatment with the CyberKnife: Marker placement and early results

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Abstract
Lung tumor tracking during stereotactic radiotherapy with the CyberKnife requires the insertion of markers in or close to the tumor. To reduce the risk of pneumothorax, three methods of marker placement were used: 1) intravascular coil placement, 2) percutaneous intrathoracal, and 3) percutaneous extrathoracal placement. We investigated the toxicity of marker placement and the tumor response of the lung tumor tracking treatment. Markers were placed in 20 patients with 22 tumors: 13 patients received a curative treatment, seven a palliative. The median Charlson Comorbidity Score was 4 (range: 1–8). Platinum fiducials and intravascular embolisation coils were used as markers. In total, 78 markers were placed: 34 intrathoracal, 23 intravascular and 21 extrathoracal. The PTV equaled the GTV+5 mm. A median dose of 45 Gy (range: 30–60 Gy, in 3 fractions) was prescribed to the 70–85% isodose. The response was evaluated with a CTscan performed 6–8 weeks after the last treatment and routinely thereafter. The median follow-up was 4 months (range: 2–11). No severe toxicity due to the marker placement was seen. Pneumothorax was not seen. The local control was 100%. Four tumors in four patients showed a complete response, 15 tumors in 14 patients a partial response, and three tumors in two patients with metastatic disease had stable disease. No severe toxicity of marker placement was seen due to the appropriate choice of one of the three methods. CyberKnife tumor tracking with markers is feasible and resulted in excellent tumor response. Longer follow-up is needed to validate the local control.

About 15 to 20% of the patients with Non Small Cell Lung Cancer (NSCLC) are diagnosed with early or localized disease [1]. The first choice of treatment is surgical resection and results in five-year survival rates of 60 to70% and a local control rate of 80% [2,3]. However, patients with comorbid illnesses like COPD and cardiovascular diseases are often no surgical candidates and these medically inoperable patients were often treated by conventional radiotherapy with doses of 60–66 Gy. This treatment resulted in 5-year survival rates of 6–30%, with local control rates of 40–70% [4–7]. The poor local control rates could be a consequence of insufficient dose administration [8,9] and/or a geographical miss due to the variable target motion [10,11].

Higher biological doses can be delivered with stereotactic radiotherapy. However, it requires the reduction of the margin used to expand the clinical target volume (CTV) to the planning target volume (PTV). A reduction in the setup margin can be achieved by immobilizing the patient with a non-invasive body frame [12,13] and/or by using image guided positioning [14]. The use of deep inspiration breath hold [15] and gating [16,17] is a method to reduce internal target volume (ITV). This is a volume that incorporates the motion of the clinical target volume (CTV). The CyberKnife with the Synchrony system can reduce the set up margin. An extra margin for tumor motion is not necessary due to its tumor tracking system.

The CyberKnife is a frameless image-guided radiotherapy system involving a 6 MV linear accelerator mounted on a robotic arm possessing six degrees of freedom. The imaging system uses two diagnostic x-ray sources mounted to the ceiling

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paired with amorphous silicon detectors to acquire live digital radiographic images of the patient. The Synchrony system requires the insertion of markers in or near the lung tumor which are used to define the position of the tumor. Using the Synchrony system, light-emitting diodes (LEDs) are placed on the patients' belly. Their motion with the respiratory cycle is registered by a camera array.

The Synchrony system identifies a correspondence model between the movement of the markers and the LEDs, representing the internal motion and the external motion, respectively. This model enables the linear accelerator to continuously track the motion of the markers via the motion of the LEDs, thereby adjusting automatically the position of the beam relative to the moving target. This correspondence model is continuously updated throughout the treatment.

Depending on the risk of pneumothorax in this group of patients with high comorbidity, three methods of marker placement were used: 1) intravascular coil placement, 2) percutaneous intrathoracal, and 3) percutaneous extrathoracal placement. We investigated the toxicity of marker placement and the tumor response of the lung tumor tracking treatment with the CyberKnife.

Methods and materials

Patient demographics

Markers were placed in or around 22 peripheral tumors in 20 patients: 13 patients had early stage lung cancer and received a curative treatment, and seven other patients with nine tumors received a palliative treatment. To evaluate the comorbidity of the patients, the Charlson Comorbidity Scale was used (Table I). In this inoperable population, five patients had the Charlson Comorbidity Score of 1–2, six patients 3–4 and nine patients more than 4 [18]. The median age for the whole group was 73 years (range: 27–89 years). Of the 13 patients with early stage lung cancer, nine had the diagnosis of lung cancer based on cytology or histology. The details of these groups are described in Table II.

Table I. The Charlson Comorbidity Scale.

Comorbidity Scale	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes (without complications)	1
Diabetes with end-organ damage	2
Hemiplegia	2
Moderate or severe renal disease	2
Second solid tumor (non-metastatic)	2
Leukemia	2
Lymphoma, multiple myeloma	2
Moderate or severe liver disease	3
Second metastatic solid tumor	6
Acquired immunodeficiency syndrome	6

Marker placement

Three different methods of marker placement were used: 1) percutaneous intrathoracal, 2) intravascular coil placement, and 3) percutaneous extrathoracal placement.

With the percutaneous intrathoracal method, three platinum fiducials (length 4 mm, thickness 0.9 mm) were placed into, or adjacent to the tumor. The procedure was done using an 18 gauge needle under fluoroscopic, CTscan or ultrasound guidance using local anesthesia. Directly after the last fiducial placement and one hour later, an anterioposterior inspiratory chest radiograph was made to diagnose a pneumothorax. For the intravascular coil method, three vascular embolisation coils (Tornado® 4/3, Cook, Bloomington, IN) were inserted into small subsegmental pulmonary end branches in or adjacent to the tumor, using a transcatheter approach. The pulmonary artery catheter was inserted through the femoral vein in the groin under local anesthesia and by using ECG-monitoring. After the insertion of the coils the patient was observed during a few hours to detect any post-punction bleeding.

With the percutaneous extrathoracal method, five platinum fiducials were placed against the ribs in the neighbourhood of the tumor under fluoroscopic guidance using an 18 gauch needle with local anesthesia. This method was chosen if a tumor was fixed against the thorax.

Table II. Patient demographics.

	Curative patients	Palliative patients
Stage T1N0M0	4	0
Stage T2N0M0	8	0
Stage T3N0M0	1	0
Recurrent lung cancer	0	2
Metastatic lung cancer	0	2
Metastatic non-lung cancer	0	3
Age (range)	75 (63–89)	62 (27–81)
Charlson Comorbidity 1–2	5	0
Charlson Comorbidity 3–4	6	0
Charlson Comorbidity >4	2	7

For the intrathoracal fiducial placement and the intravascular coil placement, the distance of the marker to the tumor border was measured if the marker was not placed inside the tumor.

The percutaneaous intrathoracal method was the first method of choice, however if the pulmonary function was too bad or the condition of the patient was poor then the intravascular coil method was used.

Radiotherapy treatment

Four to seven days after marker placement, a planning CTscan was made and the GTV was contoured on a 4-D CTscan. The PTV equaled the GTV plus 5 mm. For curative treatment, a total dose of 36 Gy (1 patient), 45 Gy (8 patients) or 60 Gy (4 patients) was prescribed to the 80–85% isodose line and was given in 3 fractions. For palliative treatment, a median dose of 45 Gy, given in 3 fractions, (range: 30–49 Gy) was prescribed to the 70–80%. One palliative patient received a total dose of 49 Gy in 7 fractions. The response according to the modified RECIST method was evaluated with a CTscan 6–8 weeks after the last treatment and routinely thereafter. The median follow-up was 4 months (range: 2–11).

Results

Marker placement

In total, 78 markers were placed. Thirty four intrathoracal fiducials were placed in or around ten tumors in the lung of ten patients. A median number of three intrathoracal fiducials per tumor were placed (range: 2–5). Twenty five fiducials in seven patients were placed by the radiation oncologist, nine fiducials in three patients by the interventional radiologist. Twenty seven markers were placed in the tumor, seven outside the tumor. The median distance of the fiducials to the tumor border was 9 mm (range: 1–22 mm). No pneumothorax or other side effects were seen.

Twenty three intravascular coils were placed in or around eight tumors in the lung of six patients. All intravascular coils were placed by the interventional radiologist. A median number of three coils were placed in or around the tumors (range: 2–4). Six intravascular coils were placed in the tumor, 17 outside the tumor. The median distance of the coils to the edge of the tumor was 11 mm (range: 4–21 mm). One patient complained of severe pleural pain 4 hours after placement that disappeared after 7 days.

Twenty one extrathoracal fiducials were placed in four patients (median per tumor: 5; range: 5–6). All extrathoracal fiducials were placed by the radiation oncologist. No side effects of this method were seen.

Tumor response

The local control was 100%. Four tumors in four patients had a complete response after a median time of 6.8 months, 15 tumors in 14 patients had a partial response after a median time of 3.5 months. Three tumors in two patients with metastatic disease had stable disease after a median time of 2 months. Three patients complained of intrathoracal pain 2–3 weeks after the treatment that disappeared with NSAIDs. No other side effects were seen. None of the patients complained of increased shortness of breath.

Discussion

Based on the selection of a particular insertion technique in function of the risk and consequence of a pneumothorax, all patients could be treated. The biggest disadvantage of the percutaneous intrathoracal placement is the risk for pneumothorax. In this category of patients, a large pneumothorax could be fatal for some of these comorbid patients. Therefore, the patients with a bad pulmonary function were selected to be implanted with intravascular coils. With the intravascular coil method, a pneumothorax has not been reported [19,20] and therefore the patients who previously had undergone a pneumectomy could be treated with the CyberKnife. With the percutaneous intrathoracal method, we reported no side effects. However, a pneumothorax after marker placement has been described. Whyte et al. noticed four complications related to percutaneous placement of two to four cylindrical gold metal fiducials (1mm in diameter by 3 mm in length) into, or adjacent to tumor, in a total of 23 patients. Three patients had pneumothoraces; two were managed expectantly, but one, who had a prior contralateral pneumonectomy, required urgent chest tube placement. One patient had exacerbation of his underlying chronic obstructive pulmonary disease [21]. A review by Rosenweig and Covey of percutaneous lung biopsy (comparable in risk to a percutaneous marker insertion) found that 23% of patients had postbiopsy pneumothorax, and of these, 7% required treatment [16]. Although 34 intrathoracal punctures were performed, we saw no pneumothorax. This is very low. More clinical use of our methods will show us if this is related to beginners' luck or the excellent staff of the interventional radiology department that selects the patients for the intravascular coil method or the percutaneous intrathoracal method.

With the intravascular coil placement, side effects like pulmonary infarcts (5%), pleuritic chest pain (33%) and groin hematoma (3%) are described [19,20]. In our patients group, we only saw severe pleuritic chest pain in one patient.

No side effects were seen with the percutaneous extrathoracal placement. We also do not expect side effects with this method.

Besides these three methods of placement, there is also the bronchoscopic placement: The marker (1.5 mm in diameter) was fixed into the bronchial tree and had an accuracy of 2 mm during the 1–2-week treatment period. They also noted that the markers were better fixed in the smaller bronchial lumens than those in the larger lumens [22]. The fiducial tracking system of the CyberKnife is very accurate. If one fiducial has moved regarding to the other fiducials then the operator will be notified by the tracking system. Before the treatment can be started the operator has to disable the fiducial so that the migrated fiducial will not be used to locate and track the tumor. So, as long as more than two fiducials are used, migration of the markers is noticed early and irradiation of a wrong target is therefore prevented. In our patient population, we did not have to reinsert fiducials due to marker migration. The migration of intravascular coils is not possible because they are clotted into a small blood vessel. Six coils were placed in the tumor. Seventeen coils were placed outside the tumor with a median distance of 11 mm (range 4–21 mm) from the edge from the tumor. Because these coils were placed in the vicinity of the tumor, they moved together with the tumor as was seen on fluoroscopy.

The excellent tumor response shows us that the Synchrony system of the CyberKnife is able to irradiate the tumor. However, our follow-up is short and longer follow-up is needed to validate the local control.

No severe toxicity of marker placement was seen due to the appropriate selection of one of the three methods: 1) intravascular coil placement, 2) percutaneous intrathoracal and 3) percutaneous extrathoracal placement. Even in this group of patients with very poor condition, CyberKnife tumor tracking with markers is feasible and resulted in excellent tumor response.

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