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ORIGINAL ARTICLE

Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small-cell lung cancer (NSCLC)

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Abstra

Stereota tes with low risk of se rable patients . A mean total d Imm ure foil (Medica e thoracic and abd Clinical target v ET. Organ moveme e added as safety m as enclosed by the 6 ng in an

Nineteen patients died, with eight patients due to cancer (12%), two to local tumor progression alone. Cancer-specific survival is 96%, 82% and 73% at 1, 2 and 3 years. Eleven patients died from comorbidities, making a 53% overall 3-year survival. Fifty five percent of the patients were affected by mild acute and subacute side effects, with only 3% experiencing pneumonitis III°. Late effects were pneumonitis III° in 1%, rib fractures in 3%, and benign pleural effusion in 2 patients. Hypofractionated SRT is safe even in elderly patients with stage I NSCLC and significantly reduced lung capacity. It leads to high local control rates and should be offered to patients not amenable for curative resection.

In stage I non-small-cell lung cancer (NSCLC) standard treatment is still surgery, in younger patients sometimes followed by systemic chemotherapy [1], [2]. The 5-year overall survival rates for pathological stage I range between 67% for pT1pN0 and 57% for pT2pN0 tumors. Based on clinical staging the corresponding values are 61% for cT1cN0 and 37% for cT2cN0, respectively. At 3 years, mean overall survival rates of about 70% in stage IA and of less than 50% in stage IB were published [3–5].

Local tumor control is about 90% and depends on the type of resection. Lobectomy and pneumo e worse outcome failure rate but mair arly NSCLC stages w definitive RT alone m nally fractiona les the results a reported 5-year

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involvement of locoregional lymph nodes is comparatively low [10]. Nevertheless, it is suggested to perform the initial staging with FDG-PET to exclude mediastinal lymph node metastases. With a negative predictive value of about 98% a tumor infiltration can be excluded by FDG-PET and computed tomography with very high probability [11], [12].

Now, we present our current data on local tumor control, overall survival and early and late toxicity after hSRT in stage I non-small cell lung cancer. In all patients FDG-PET was applied as basic staging procedure and to define target volume, especially in tumor producing subsequent atelectasis. All patients had daily planning-CT in treatment position before each fraction.

Material and methods

Study design

This was a Phase I/II non-randomized trial. All patients underwent radiation treatment in curative intention. Baseline evaluations were performed before initiation of therapy: complete medical history; physical including cardiovascular examination and lung function test; determination of the ECOG performance status; full blood counts and biochem G-PET was used for nd to define the exte eural effusion patients underwe e-needle aspiratic

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Study e

The primary end points of the study were clinical outcome defined according to the World Health Organization for response (local control defined as complete or partial remission as well as stable disease) as well as overall and cancer-specific survival. Acute and late toxicity were additional endpoints, mainly acute lung toxicity >CTC° I.

Radiotherapy

In the first eight patients, we used sequential CT-scans to define the accuracy and reproducibility of patient positioning in the commercially available vacuum couch (Medical Intelligence). CT-scans were superimposed by using the ExacTrak system (BrainLab) that produces errors of less than 1 mm using at least four markers. Reproducibility of the vacuum couch system was good, with mean deviations of 2.4 (0–5.5) mm in ventro-dorsal (y-axis) and 3.4 (1–5) mm in lateral direction (x-axis) only, but mean cranio-caudal deviation of 8 (2–15) mm (z-axis). The latter considerable error was a systematic one in cranial direction, likely caused by shrinkage of the vacuum couch within the first hours after preparation. Therefore, we introduced an interval of at least one day after preparation of couch before the planning CT-scan was carried out. By this, systematic errors could be avoided, and the random error was reduced to 3.5 (+/−1) mm in x, 1.5 (+/−1.0) mm in y-, and 1.5 (+/−1.0) mm in z-axis. Nevertheless, those deviations supported the evidence of the necessity of repeated CT-scan directly before each treatment session, to correct errors immediately before each fraction [13].

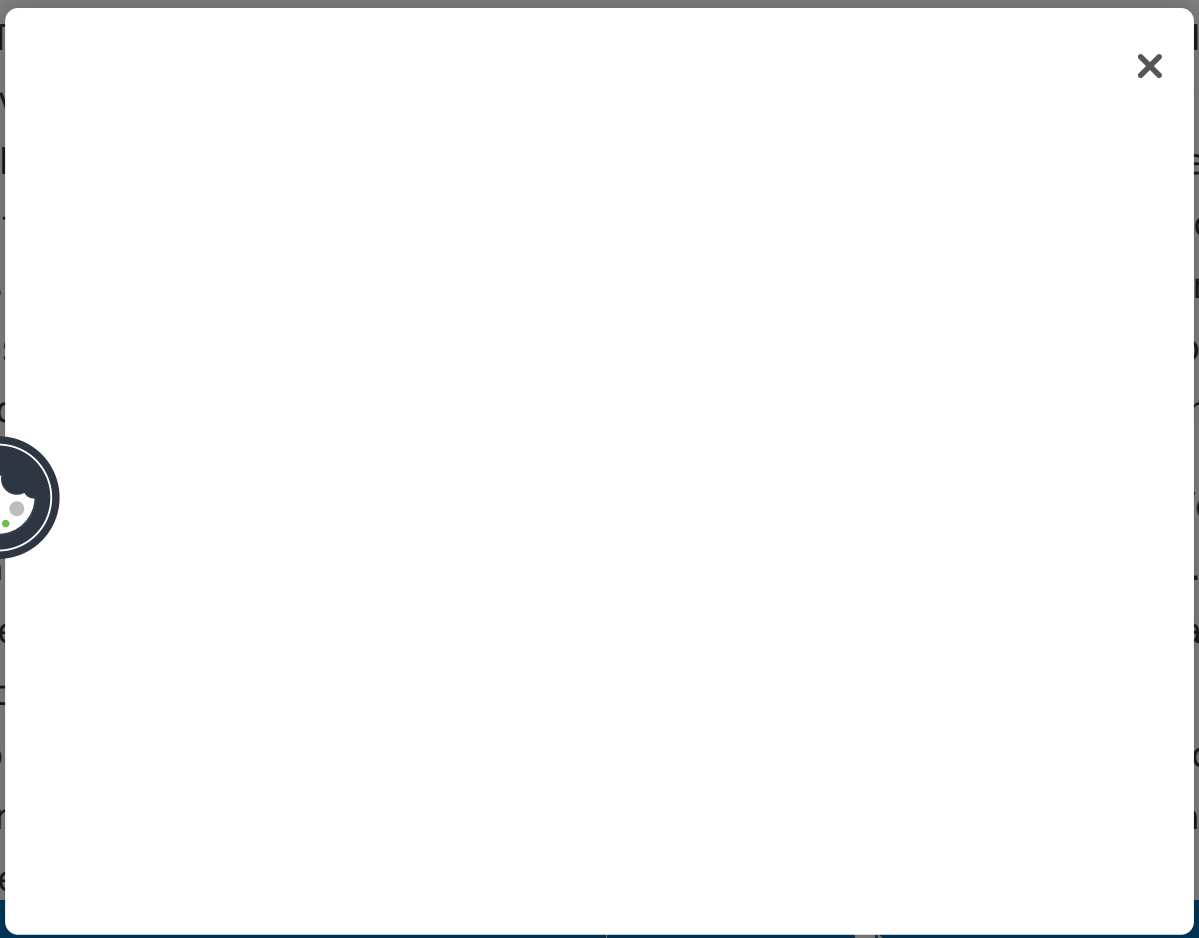
Within th ntion, starting dose to 30 Gy in 3 f s depended on lung ripheral tumors a times 7 Gy was the passing the plannin couch and low p

Clinical t formation of FDG-PET cious in CT but with lume. Organ moveme m, cranio-caudal 6 12 mm)

before starting treatment. The individual values were taken into account as safety margin for the definition of the PTV. The PTV was enclosed by the 60%-isodose. Slice thickness on the CT-scan was 5 mm for three-dimensional treatment planning. Irradiation was applied with multiple coplanar static beams and/or dynamic arcs. Beam shaping was performed using an integrated motorized multileaf collimator with 1 cm leaf width. Calculation was done with the Siemens Helax system with pencil beam algorithm. Dose constraints for critical organs were set for spinal cord (max. 3 times 5 Gy or 5 times 4 Gy) and esophagus (max. 3 times 7 Gy or 5 times 5.5 Gy).

Toxicity and tumor control

During treatment all patients were interviewed and clinically examined for early radiation induced side effects on a daily basis. After hSRT, tumor response was evaluated by orthogonal radiographs and/or CT at 4–6 weeks together with clinical evaluation of side effects by a patient questionnaire and clinical examination as well as lung function and blood counts. At 8–10 weeks, and 4, 7 and 12 months, later in 6 months intervals, local control and adverse effects of radiotherapy were evaluated by CT (5 mm slice thickness), lung function test, blood counts, CRP, clinical examination, and patient questionnaire. In persisting tumors more than 18 months after hSRT or locally progressing lung tumor, FDG-PET-CT was done to exclude or confirm persistent cancer. In all patients with visible tumor in CT-scan but without evidence of uptake in FDG-PET



In cases with ele with lavage, ent tumor was con cancer, patients nd broncho to three repeate malignancy.

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1. complete remission = no sign of tumor in CT-scan and/or FDG-PET and/or bronchoscopy;

2. partial remission = reduction of at least 50% in tumor volume in CT-scan and/or reduced uptake in FDG-PET;

3. local progression = increase of tumor volume of more than 25% in volume in CT-scan and/or increased uptake in FDG-PET and positive histology in bronchoscopy;

4. distant progression = metastases in locoregional lymph nodes or in distant sites proven by CT-scan and/or FDG-PET.

Toxicity was defined according to CTC/RTOG criteria during treatment up to 3 months after radiotherapy and according to RTOG/EORTC after 3 months, with grading from 0 to 4.

Statistical analysis

Cumulative survival curves were calculated and drawn using Kaplan-Meier algorithms with the day of first treatment as the starting point. Actuarial local tumor control rates were determined using the Kaplan-Meier method assuming regrowth of the irradiated tumor or persistent uptake in FDG-PET as an event, irrespective of the status of other lesions outside of the treated volume. A tumor was censored in patients who died from other dis

Result

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volume was 79 cm^3 (16–299) (Table I). Total dose was 37.5 Gy in mean (range 24–40 Gy), given in 3 to 5 fractions within 5 days (3–10 days) (Table II).

Table I. Demographics and distribution of treatment parameters.

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Table II. Dose escalation procedure (*individual decision).

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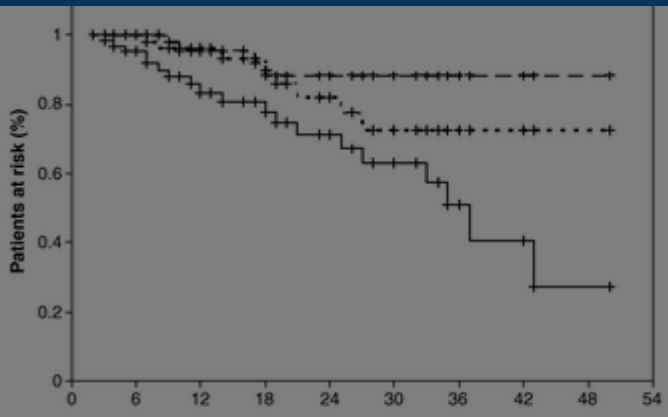
Actuarial local tumor control at 1, 2 and 3 years is 96%, 88% and 88%, respectively (Figure 1). In 26 patients second FDG-PET was carried out to confirm or exclude persistent or progressing malignant tumor. Follow-up imaging revealed a complete local response in 44 patients (64.7%), confirmed either by CT-scan alone or by CT-scan and FDG-PET. In 20 patients (29.4%) maximum response was defined as a partial remission. In four patients local progression occurred (5.9%). The patterns of first disease recurren urrences were obs

Figure 1. % at 3 years), c ears), and overall s to Kaplan-Meier).



Patients at risk (total patients n=68)

Local Control	35	29	23	17	11	5	0
Disease free survival	41	35	29	23	17	11	5
Overall survival	53	47	41	35	29	23	17

according to Kaplan Meier

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Table III. Distribution of first site of tumor recurrence and cause of death.

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Disease-specific survival is 96%, 82% and 73% at 1, 2, and 3 year follow-up (Figure 1). Eight pa gression. No patient evere comorbi , 71%, and 51% at

In gener t. Fifty percent ther clinically ere appa ymptoms and ra nly 19.2% of the pa fter hSRT. Only one ths after treatmer an 2 years in this pa

Article contents Related research

Table IV. Lung toxicity (in percent) classified by clinical symptoms and radiological signs in CT-scan (*only clinical symptoms: maximum values).

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Other side effects were fatigue (15% during or immediately after hSRT), shivering 5.1%, nausea 5.1%, and dermatitis 3.4%, with none being severe. Late effects were benign pleural effusion in 3.4%, rib fracture without confirmation of cancer in 5.0%, and a remarkable fibrosis of soft tissue of the thoracic wall in 3.4% of the patients (Table V). In total, there was no obvious dose dependence regarding acute or late radiation induced side effects.

Table V. Non-lung toxicity (in percent/absolute values).

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Discus

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accuracy of FDG-PET seems to be confirmed by our observation of a low regional failure rate during the first two years of follow-up. Only 6% of our patients developed an isolated initial tumor recurrence in hilar or mediastinal lymph nodes. These four patients could be treated in this area again, even when target volumes were overlapping, by radiotherapy or combined radiochemotherapy, resulting in a further regional tumor control for at least 12 months in all patients.

Unfortunately, data sets on overall survival with a longer follow-up after initial staging with FDG-PET-CT are still limited. This makes a direct comparison of our own data with results after curative resection as well as hSRT from other centers difficult [15]. Considering disease-specific survival data one has to be aware of the fact that these are even scarcer than results concerning overall survival. Onishi et al. (2004) were able to demonstrate in a large multicenter trial, that overall survival after hSRT is comparatively better when patients are operable but refuse resection. In this subgroup of patients 3-year survival was significantly improved to 88% when a biological effective dose of more than 100 Gy was applied. These results are even better than those usually achieved by surgical procedures.

Most patients from our institution died from other causes than lung cancer, such as heart failure, second cancer, liver cirrhosis, exacerbation of severe chronic obstructive lung disease without signs of pneumonitis, etc. This explains the poor 3-year overall survival ntrol rate at 3 years. l condition a differenc e detected followin of 32% for stage IB c survival was repo wn data.

Compar lly a distant one. distant metasta n extent NSCLC is e of addition after hSRT, such as survival has already

We will continue to improve the results for our patients with stage I NSCLC treated with hSRT by optimizing the fractionation schedule and the total dose within a following single institutional trial. Additionally in future, to patients younger than 75 years we will offer systemic chemotherapy. Also in this clinical trial, FDG-PET will continue to be the central staging procedure.

We thank the “Bavarian State Ministry of Environment, Public Health and Consumer Protection” for generous financial support.

Related Research Data

Experience of PET for target localisation in radiation oncology
Source: British Journal of Radiology
Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors
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Source: The Annals of Thoracic Surgery

Survival after resection for lung cancer is the outcome that matters

Source: The American Journal of Surgery

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Source: Cochrane Database of Systematic Reviews

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