Palliative Endobronchial Brachytherapy for Central Lung Tumors*

A Prospective, Randomized Comparison of Two Fractionation Schedules

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Aim of the study: Remote high dose rate brachytherapy is an effective local treatment modality for central lung tumors and has the potential to improve survival time. Optimal dose and fractionation schemes have not been identified yet. We conducted a prospective randomized study to compare two treatment schedules in terms of survival time, local tumor control, and possible complications.

Design: Group 1 received 4 brachtherapies with a dose of 3.8 Gy (at a 10-mm depth) on a weekly basis, and group 2 received 2 treatments with 7.2 Gy (at a 10-mm depth) at a 3-week interval. At a depth of 5 mm, the calculated doses would be 8 and 15 Gy. This study is still ongoing. Here we report interim results.

Patients: Ninety-three patients with advanced cancer were included in the study; 44 were in group 1 and 49, in group 2. Both groups were comparable regarding age, sex, tumor stage, Karnofsky performance status, and histologic findings.

Interventions: A mean total irradiation dose of 13.4 ± 5.2 Gy for group 1 and 13.7 ± 4.4 Gy for group 2 were applied (calculated at 10 mm from the source axis, equivalent to 27.9 Gy in group 1 and 28.5 Gy in group 2 at a 5-mm depth).

Results: The 1-year survival rate was 11.4% in group 1 and 20.4% in group 2. No significant difference in survival time was found, but mean survival was longer in group 2 (49 weeks) than in group 1 (26 weeks). Local control after 3 months was comparable in both groups. Fatal hemoptysis occurred at a similar rate in group 1 (22.2%) and in group 2 (21.1%).

Conclusion: High-dose rate brachytherapy with 2×7.2 Gy with a 3-week interval is equivalent to a 4×3.8-Gy regimen on a weekly basis. The shorter treatment schedule is more convenient for patients, does not cause more side effects, and provides an equal local tumor control. (Chest 1995; 107:463-70)

HDR=high dose rate; KPS=Karnofsky performance status; 192Ir=iridium 192

Key words: lung neoplasm radiotherapy; brachytherapy; prospective studies; survival analysis

Lung cancer is one of the most frequent malignant diseases in men. The incidence and mortality of lung cancer have increased significantly over the past few decades. However, in spite of tremendous therapeutic efforts no significant improvement in survival time has been achieved. Surgical resection affords a chance of cure in only 30% of all cases, depending on tumor stage. However, local recurrence with consequent fatal outcome can be avoided in only 40% of these patients. Externally radiotherapy alone holds a potential for cure for few patients, and local recurrences are even more frequent. Nevertheless, in a palliative situation external radiotherapy can improve symptoms and survival time. For patients who cannot be treated by surgery or external radiotherapy, local treatment of bronchial occlusion may be beneficial. Apart from Nd-YAG laser therapy and endoluminal prosthesis, brachytherapy is being used increasingly for the treatment of these subgroups of patients. Initially low dose rates prevailed in brachytherapy and are now replaced by high-dose rates (HDRs). Remote HDR afterloading brachytherapy with iridium 192 (192Ir) improves the effectiveness of local disease control. Moreover, HDR brachytherapy offers a convenient form of therapy owing to a short irradiation time which makes treatment on an outpatient basis possible.

For better results, we believed that fractionation schemes and total dose needed to be optimized. Therefore, we conducted a prospective randomized
study to manipulate the dose per fraction (fractionation) of HDR brachytherapy in palliative lung cancer treatment. An equal overall dose of 14.4 Gy in a 10-mm depth (equivalent to 30 Gy at a 5-mm depth) was applied. This study reports the interim results obtained up to November 1993.

**METHODS**

**Study Site**

After approval by the Ethics Committee of the School of Medicine, University of Munich, this study started in January 1989 and is ongoing.

**Patients Selection and Randomization**

Ninety-three patients were included in this study according to the following inclusion criteria: lung cancer, proven by histologic or cytologic studies; cancer localization in the trachea or in the mainstem or lobar bronchi; substantial occlusion evidenced by bronchoscopic examination; no alternative treatment options such as surgery, external radiotherapy, or chemotherapy; no concomitant tumor treatment underway; informed consent by the patient. There was no selection of patients regarding age, sex, histologic findings, tumor stage, or Karnofsky performance status (KPS).

Patients were not included if a free choice between the two treatment modalities was not possible for any reasons, eg, a treatment preference of the patient or the treating physician, or if concomitant treatment was planned during the course of our study. The randomization protocol divided the patients into two treatment groups: Each group received approximately the same overall dose of HDR brachytherapy (14.4 to 15.4 Gy) but in different fractions at different intervals. Group 1 received brachytherapy with a total dose of 15.4 Gy, delivered in 4 fractions of 3.8 Gy at 10 mm from the source axis at weekly intervals. Group 2 received brachytherapy with a total dose of 14.4 Gy in fractions of 2×7.2-Gy at 10 mm from the source axis with an interval of 3 weeks.

**Brachytherapy Procedure**

Brachytherapy was carried out mainly on an outpatient basis. Bronchoscopy was performed with the patient receiving topical anesthesia to determine the field intended for treatment. The area was marked externally by fluoroscopy. Subsequently, a guidewire was placed through the instrumentation channel of the endoscope. After removal of the bronchoscope, a shortened gastric tube with an external diameter of 5 mm was inserted by the Seldinger technique over the guidewire and placed inside the tumor bulk. The irradiation applicator was placed into the tube and taped to the tip of the nose to prevent it from being dislodged. The applicator was then connected to the ¹⁹²Ir HDR remote afterloading unit (Gammamed III, Isotopenhanteknik Dr. Sauwein, Haan, Germany). The irradiation source (diameter, 1 mm) was advanced to the intended position under computer control and then drawn backward at intervals of 5-mm distance. It remained in each position for the time needed to apply the computed dose. By this method, a field of high irradiation dose is built up in the center with a fast decrease toward the periphery.

All doses reported were originally calculated at a distance of 5 mm from the source axis. To convert those doses to a distance of 10-mm depth, multiplication by 0.48 is necessary. The application time ranged from 2 to 15 min, depending on the length of the irradiated area, the delivered dose, and the actual activity of the ¹⁹²Ir source.

**Medical Data and Follow-up Study**

Prior to randomization, blood samples, lung function tests, fiberoptic bronchoscopy, plain chest radiographs, and computed tomographic scans of the chest were carried out to serve as baseline measurements for each patient. Upon entering the study, all patients were staged according to the international staging system for lung cancer as recommended by the American Joint Committee on Cancer. Histologic classification was done following the guidelines of the World Health Organization. The KPS was registered at the beginning and at the end of endoluminal irradiation.

After 3 months, a control bronchoscopic examination and a chest radiograph were performed to evaluate local control and tumor response. Local control of the tumor was defined as follows: tumor recurrence was characterized as disappearance and regrowth of tumor; tumor progression, as persistent and further growth of tumor; no change, as persistent or arrested tumor size. Complete or partial remission was defined as no evidence of tumor or more than 25% tumor reduction. If treatment failure was evident during the follow-up period, an additional course of brachytherapy was allowed by the protocol. Every patient participated in the follow-up study at defined intervals. Cause of death was documented in each case. Fatal hemoptysis was defined as massive bleeding from the tracheobronchial tree leading to death. A local intrathoracic problem was encountered when complications such as occlusion, pneumonia, or intrapulmonary metastasis were the main cause of death. Systemic complications were defined as distant metastasis causing death. Tumor unrelated disease or unknown causes were subsumed as other causes.

**End Point**

Survival time was considered the endpoint of the study and defined as the time from the beginning of the study to the patient's death. Assessment of local tumor control provided a second endpoint. The KPS was used as parameter of the acute effect of brachytherapy.

**Statistics**

All cases were analyzed on an intention-to-treat basis. For survival analysis, we included primarily all patients treated. Then we analyzed separately those patients who fully completed our treatment protocol. Differences between both groups were considered significant with a probability value of less than 0.05; for data at the ordinal level, we used the χ² test and the Mann-Whitney U test for independent samples; data at the interval level were calculated with the Student t test for independent samples. Survival plots are created using the procedure of Kaplan and Meier, testing the differences in survival time was done with the log rank test. All statistical analysis was calculated with the Statistical Package for Social Science SPSS/PC for Windows 5.02.

**RESULTS**

**Clinical Data**

Ninety-three patients were included in this study; 44 subjects were in group 1 (4×3.8 Gy) and 49 were in group 2 (2×7.2 Gy). The minimum observation time was 3 months with a median observation time of 2.5 years. The main demographic and medical data are shown in Table 1. Group 1 consisted of 36 (81.8%) men and 8 (18.2%) women and group 2 consisted of 34 (69.4%) men and 15 (30.6%) women. The mean age was 66.2 ± 10.4 in group 1 and 64.0 ± 10.3 in group 2. Most patients had a very ad-
advanced tumor stage; only 27.7% in group 1 and 16.3% in group 2 had tumor stages below IIIB. In both groups, the number of patients with metastatic disease was not significantly different (group 1, 15 patients; group 2, 23 patients). Recurrent tumor from pretreated patients was present in 13 (29.5%) patients in group 1 and in 11 (22.4%) patients in group 2.

The two major histologic types in the biopsies obtained were squamous cell cancer (52.3 and 46.9%, respectively) and adenocarcinoma (18.1 and 22.4%). In group 2, two patients (4.1%) with adenoid-cystic carcinoma were included in the evaluation.

In Group 1, 88.9% and in group 2, 92.7% of the patients had undergone pretreatment. The two most important treatment modalities were external radiotherapy (group 1, 47.2%, mean irradiation dose of 41.8 Gy; group 2, 39%, mean irradiation dose of 52.3 Gy) and the use of a Nd-YAG laser (33.3% and 46.3%). More than 40% in each group underwent different combinations of these treatments. A mean KPS of 60 (range, 25 to 90) in both groups illustrates the poor performance status of these patients. The mean KPS increased after treatment to 63.8 (range, 35 to 90) and 65.7 (range, 30 to 90), respectively, indicating that this form of irradiation causes very little discomfort to the patients. The proximal localization of the afterloading probe was almost identical in both groups as shown in Table 1. The most frequent localization sites were the carina and the two mainstem bronchi.

The total irradiation dose applied was slightly lower in group 1 (13.4 ± 4.4 Gy) than in group 2 (13.7 ± 4.3 Gy). The main reason for deviation from protocol was the death of 6 patients in group 1 and 11 patients in group 2 (8.2% and 10.2%).

Table 1—Main Anthropometric and Medical Data of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=44)</th>
<th>Group 2 (n=49)</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, years ± SE</td>
<td>66.25 ± 10.4</td>
<td>64.02 ± 10.3</td>
<td>NS†</td>
</tr>
<tr>
<td>Range, years ± SE</td>
<td>39-86</td>
<td>45-88</td>
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</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81.8%</td>
<td>69.4%</td>
<td>NS†</td>
</tr>
<tr>
<td>Female</td>
<td>18.4%</td>
<td>30.6%</td>
<td>NS†</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Beginning of Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>60.7 ± 10.5</td>
<td>60.0 ± 14.0</td>
<td>NS†</td>
</tr>
<tr>
<td>Range</td>
<td>40-85</td>
<td>25-90</td>
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</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>63.8 ± 13.0</td>
<td>65.7 ± 14.6</td>
<td>NS†</td>
</tr>
<tr>
<td>Range</td>
<td>30-90</td>
<td>30-90</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor stage at study entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (2.3%)</td>
<td>1 (2.0%)</td>
<td>NS†</td>
</tr>
<tr>
<td>II</td>
<td>2 (4.5%)</td>
<td>1 (2.0%)</td>
<td>NS†</td>
</tr>
<tr>
<td>III A</td>
<td>8 (18.2%)</td>
<td>7 (14.3%)</td>
<td>NS†</td>
</tr>
<tr>
<td>III B</td>
<td>12 (27.2%)</td>
<td>9 (16.3%)</td>
<td>NS†</td>
</tr>
<tr>
<td>IV</td>
<td>21 (47.7%)</td>
<td>32 (65.3%)</td>
<td>NS†</td>
</tr>
<tr>
<td><strong>Histologic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>23 (52.3%)</td>
<td>23 (46.9%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Adeno</td>
<td>8 (18.2%)</td>
<td>11 (22.4%)</td>
<td>NS†</td>
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<tr>
<td>Large-Cell</td>
<td>4 (9.1%)</td>
<td>4 (8.2%)</td>
<td>NS†</td>
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<tr>
<td>Oat Cell</td>
<td>8 (18.2%)</td>
<td>8 (16.5%)</td>
<td>NS†</td>
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<tr>
<td>Adenoid-cystic</td>
<td>...</td>
<td>2 (4.1%)</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.3%)</td>
<td>5 (10.2%)</td>
<td>NS†</td>
</tr>
<tr>
<td><strong>Treatment before entering the study more than 100% because of different treatment combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11.1%</td>
<td>7.3%</td>
<td>NS†</td>
</tr>
<tr>
<td>Surgery</td>
<td>19.4%</td>
<td>19.4%</td>
<td>NS†</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>11.1%</td>
<td>17.0%</td>
<td>NS†</td>
</tr>
<tr>
<td>Ext. irradiation</td>
<td>47.2%</td>
<td>39.0%</td>
<td>NS†</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>30.5%</td>
<td>16.9%</td>
<td>NS†</td>
</tr>
<tr>
<td>N-D-YAG laser</td>
<td>33.3%</td>
<td>46.3%</td>
<td>NS†</td>
</tr>
<tr>
<td>Stent</td>
<td>2.8%</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Combinations of the above</td>
<td>46.0%</td>
<td>43.7%</td>
<td>NS†</td>
</tr>
<tr>
<td><strong>Proximal localization of the irradiation probe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>8 (18.2%)</td>
<td>13 (26.5%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Mainstem bronchi</td>
<td>30 (68.2%)</td>
<td>28 (57.1%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Distal bronchi</td>
<td>6 (13.6%)</td>
<td>8 (16.3%)</td>
<td>NS†</td>
</tr>
</tbody>
</table>

*NS = not significant.
†Significance calculated with Student t test.
‡Significance calculated with x² test.
Table 2—Irradiation Dose in Groups 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=44)</th>
<th>Group 2 (n=49)</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean irradiation dose, Gy</td>
<td>13.4 ± 5.2</td>
<td>13.7 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Irradiation less than</td>
<td>27.2%</td>
<td>14.3%</td>
<td>NS</td>
</tr>
<tr>
<td>14.4/15.4 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full dose, 14.4/15.4 Gy</td>
<td>70.4%</td>
<td>79.6%</td>
<td>NS</td>
</tr>
<tr>
<td>More than 14.4/15.4 Gy</td>
<td>2.2%</td>
<td>6.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values determined by $\chi^2$ and Student $t$ tests. NS = not significant.

Irradiation values = 14.4 Gy for Group 1; 15.4 Gy for Group 2.

5 patients in group 2 within the treatment period and deterioration of a further 6 and 2 patients, respectively, which did not allow treatment according to protocol (Table 2). Eight of 44 (18.2%) patients in group 1 and 11 of 49 (22.4%) in group 2 received further treatment, e.g., chemotherapy, laser coagulation, or repeated brachytherapy, after the study treatment was completed.

Survival

The 1-year survival rate was 11.4% (5 of 44) in group 1 and 20.4% (10 of 49) in group 2. Survival after 6 months was 13 of 44 (29.5%) and 16 of 49 (32.7%), respectively. These percentages remained valid even after the data were corrected for differences in histologic findings or tumor stage. The mean survival time reached 49 weeks in group 2, while group 1 had a lower mean survival of 26 weeks. This finding indicates a trend, but in both groups median survival was almost equal (19 vs 18 weeks), so no significant probability level was reached (Fig 1).

This result remained stable, when only those patients who were treated according to protocol were analyzed. In group 1 median survival increased slightly to 20 weeks (mean, 30 weeks), whereas the median survival time in group 2 was 24 weeks (mean, 55). The probability value was now 0.29 (Fig 2). One interesting finding is the difference in survival when we look at the histologic types of tumor. The survival chart and log rank test of patients with squamous cell cancer suggests an advantage in median survival (19 vs 9 weeks) for group 1 (Fig 3).

Group 2, however, shows an almost significantly (p=0.07) longer mean (71 vs 27 weeks) and median (33 vs 12 weeks) survival when squamous cell tumors were dropped from analysis. Median survival here is 3 times longer than in group 1.

Causes of Death

Causes of death in both groups are shown in Figure 4. The main reason for death was tumor growth in both groups, with no significant differences between local growth and systemic spread in groups 1 and 2. While in group 1 more patients died from systemic spread, in group 2 death from local tumor progression or systemic spread was distributed evenly. Fatal hemoptysis was the cause of death in 20% of all

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21708/)

**Figure 1.** Survival in groups 1 and 2, Kaplan-Meier-plot; in group 1, 4 patients were censored, and in group 2, 10 patients were censored. Mean survival in group 1 was 26 weeks and in group 2, it was 49 weeks.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21708/)

**Figure 2.** Survival in groups 1 and 2, Kaplan-Meier-plot; all patients with 30 Gy or more of endoluminal irradiation. Mean survival in group 1 was 30 weeks, and in group 2, it was 55 weeks; in each group, 5 patients were censored.

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21708/)

**Figure 3.** Survival in groups 1 and 2, Kaplan-Meier-plot, with only squamous cell cancers; in each group, 1 patient was censored.

Palliative Endobronchial Brachytherapy for Lung Tumors (Huber et al)
cases, with almost equal numbers in both groups. If the study population is analyzed on a protocol basis, bleeding from cancer was 31.8% (7 patients) in group 1 and 17.2% (5 patients) in group 2. These differences are not significant yet.

Survival time in relation to causes of death is shown in Table 3. Although no difference reaches significance, a trend may be seen for shorter median but not mean survival in group II regarding the time span until bleeding occurred from the tracheobronchial tree.

Local Tumor Control

Local tumor control was assessed 3 months after the end of the treatment. Out of 93 patients, 73 (79%) could be evaluated at this time. Some patients dropped out due to early death within the first three months. Complete remission was seen in one patient in group 1. The criteria for partial remission were met by 15 (41.6) patients in group 1 and by 18 (48.6) patients in group 2. No change of tumor growth was found in group 1 in 2 (5.5%) patients and in 7 (19%) patients in group 2. Tumor progression was seen in 15 patients in each group.

To obtain data about the influence of the dose rate applied and possible side effects, we looked at the time span between source replacement of the afterloading unit and treatment. A fresh source has an initial dose rate around 760 cGy/min; after 2.5 months, this rate declines to 378 cGy/min (the half life of the source is 74 days). In group 1, the time interval from source replacement to treatment date was slightly higher than in group 2, but not significantly (group 1-mean, 10.25 ± 4.09 weeks; median, 10.5 weeks; and group 2-mean, 8.54 ± 5.3 median, 8.5). These data were related to the cause of death and survival time. However, we could not detect an influence of these parameters on patients who underwent brachytherapy 1 or 2 weeks after source replacement. At this point, the administered dose rate was about 4 times higher than the dose rate in patients receiving therapy at 16 weeks after replacement.

Likewise, if we looked for changes in survival or episodes of bleeding in patients receiving irradiation at an average of at least 10 weeks after source replacement, there were no significant differences.

Discussion

The results presented are based on a study population of 93 patients with far advanced lung cancer. Our investigation shows no disadvantage for the fractionation regimen employing 2 times 7.2 Gy with a 3-week interval when compared with a more fractionated schedule (4X3.8 Gy weekly). Survival time in the group receiving two applications is not significantly higher than with the more fractionated schedule, but the trend toward longer survival is obvious. Local disease control and side effects are similar in both groups. The distribution of sex and age in our study groups reflects the general distribution in larger series of lung cancers.\textsuperscript{1,3}

An important prognostic factor for survival time of patients is their KPS during treatment. In a previous study,\textsuperscript{26} it was shown that a KPS lower than 90 is a most unfavorable parameter regarding survival. In our study, only one of our patients had a KPS of 90 at the beginning of the study (at the end of treatment there were five patients). This could explain the short overall survival time. The mean KPS improved moderately after treatment. This indicates the lack of serious acute side effects of this treatment modality. Furthermore, the improvement of local tumor control also improves the general well-being of our patients.

Regarding the types of histologic characteristics of the trial patients, again the distribution is almost the same as in the larger series of lung cancer patients. We accepted every kind of histologic feature because in this late stage of cancer disease local treatment of every kind of tumor often is necessary, regardless of the potentially higher malignancy of some cell types. In both groups, the number of squamous cell carcinoma was exactly the same, about 50% of the patients. As the characteristics of this subgroup were
comparable with the whole population, we analyzed survival in this subgroup. In contrast to the overall result obtained, group 1 had a higher median survival. Explanation of this finding is difficult because studies about tumor cell biology regarding the influence of cell type and method of radiation are missing. We tried to do a meta-analysis of previous studies in terms of survival time, type of radiation, and tumor cell type. However, histologic typing is seldom specified, so retrospective conclusions are not possible.

Small cell tumors in general have a shorter survival time than the other carcinomas. In our study, small cell tumors were more frequent in group 1. However, if survival was analyzed with or without this subgroup, no change was found in group 1. Nevertheless, there was a slight deterioration of survival in group 2 if oat cell tumors were dropped. This shows that there is no significant effect of the histologic findings on survival or cause of death in our study population.

To exclude another possible bias, we looked at the tumor stage at the beginning of our study. Almost all patients had a far advanced tumor stage. This is of course related to our inclusion criteria, that no other treatment modalities were suitable at the beginning of our study. Furthermore, about 90% had undergone prior treatments. Median survival time in our patients was about 4.5 months, not even half a year. This demonstrates one crucial point for studies like this. It is difficult to detect an unequivocal difference comparing treatment regimens when patients are studied who have a relatively short survival time. It can be assumed, though, that dying without therapy would be quite faster and more painful, especially in lung cancer. Other studies and this one show clearly that good local control of the tumor can be obtained for a reasonably long time (in relation to the survival time left), and that some treatment modalities even seem to improve survival time. Median survival in the previously mentioned studies ranged from 2 to 10 months, but influencing variables are not shown. This improvement in survival time for one of the treatment regimens cannot be shown in our study on a large series of patients. However, we can make a statement about the required dose and fractionation in end-stage central lung cancer: two irradiations with two times 7.2 Gy are enough to obtain the same or even a better result compared with four times half the dose.

The most important potential side effect of brachytherapy seems to be fatal hemoptysis. In some previous studies, causes of death are shown, but the occurrence of fatal hemoptysis is considered as a complication of treatment and not related to the disease itself. It is not clear if the incidence of lethal hemoptysis is related, for example, to tumor invasion into pulmonary vessels or related to the administered irradiation dose and fractionation regimen. Following Cox et al., hemoptysis is the cause of death in lung cancer patients depending on cell type in about 2 to 8% of all cases when external irradiation was applied. In a large sample, the number of fatal bleedings was 3.3%, irrespective of treatment modality. There was a correlation of this complication with squamous cell histologic features and tumor localization on mainstem bronchi. This localization, which was part of the inclusion criteria in our study, represents a further negative selection toward more frequent hemorrhages. In our study population, the frequency of fatal bleeding from the tracheobronchial tree was 15% and accounted for approximately 22% of all causes of death. When regarding squamous cell tumors, we saw bleeding in 11 (29.7%) cases, 5 (31.3%) occurred in group 1 and 6 (28.6%) in group 2; however, only 5 (14.6%) patients in our study population had other histologic features. Compared with other studies, the incidence of hemorrhage is slightly higher. This might be due to different selection criteria concerning localization and histologic characteristics. The incidence is high enough, however, to strengthen all efforts to minimize potential side effects.

Speiser and Spratling recently published a study with a large series of patients in order to find the optimum dose and fractionation in brachytherapy for central lung cancer. They treated their patients without randomization. Different treatment regimens were tested subsequently with three levels of brachytherapy doses. Regardless of the limitations of their methods their conclusion is that the most effective dose and fractionation is 7.5 Gy in a 10-mm depth for 3 fractions in a week. There was no difference in survival time (median survival from first treatment, about 25 weeks) in all three treatment groups. To our group 2, only 66% of the preferred treatment dose of Speiser and Spratling was applied (2×7.2 Gy), but median survival time is comparable. We conclude that two fractions of 7.2 Gy is enough to obtain reasonable local control until the death of the patient and that more treatment would induce more possible side effects, increase treatment cost, and be more inconvenient for patients.

CONCLUSION

In this prospective and randomized study, 93 patients were evaluated and distributed in two treatment groups, one receiving 15.4 Gy in 4 fractions of 3.8 Gy and, the other receiving 14.4 Gy in 2 fractions of 7.2 Gy. The overall survival is slightly better for group 2, but median survival time is the same. Local control is a little better in group 1, but this has no
influence on survival time. Occurrence of fatal hemorrhages also is equal in both groups, depending on the types of histologic findings.

At present, we can show that brachytherapy for central lung tumors with palliative intent can be done with good results regarding survival and local control with only two sessions of 7.2 Gy each. This seems to be the most convenient and safest treatment modality for patients with these tumors. This statement must be made with caution owing to the limited number of patients in our trial; comparison with other studies is difficult because of different study designs, applied dosages, and fractionation schedules.

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REFERENCES
19 Stout R. Endobronchial brachytherapy. Lung Cancer 1993; 9:295-300
26 Cox JD, Komaki R, Eierst DR. Irradiation for inoperable carcinoma of the lung and high performance status. JAMA 1980; 17:31-33