Curative Irradiation of Limited Endobronchial Carcinomas With High-Dose Rate Brachytherapy

Results of a Pilot Study

Maurice Pérol, MD; Raffaele Caliandro, MD; Pascal Pommier, MD; Claude Malet, PhD; Xavier Montbarbon, MD; Christian Carrie, MD; and Jean Michel Ardiet, MD

Objectives of the study: Pilot study to assess high-dose rate (HDR) brachytherapy as sole treatment for limited endobronchial non-small cell lung carcinomas.

Inclusion criteria: Proximal non-small cell lung cancer in a not previously irradiated area, with a maximal diameter of 1 cm, no visible tumor on CT scan, lack of other treatment options in patients with severe, chronic respiratory failure, surgery, or external radiotherapy for a previous lung cancer.

Treatment protocol: Treatment was based on an escalating dose protocol. Patients received three to five fractions of 7 Gy prescribed at 10 mm from the center of the applicator, once a week.

Results: Nineteen patients were included in this trial. The first two patients received three fractions of 7 Gy, the four next patients received four fractions, and the 13 remaining patients were treated with five fractions of 7 Gy. Two months after the end of the procedure, tumors in 15 of 18 evaluable patients (83%) were locally controlled with negative results of biopsies. At 1 year, local control was still obtained in 12 of 16 evaluable patients (75%). With a mean follow-up of 28 months, 1-year and 2-year actuarial survival rates were 78% and 58%, respectively, with a 28-month median survival. One patient with local control died from hemoptysis 12 months after treatment. Two patients suffered from severe necrosis of the bronchial wall; one of them died from hemoptysis.

Conclusion: HDR brachytherapy is an effective treatment for small endobronchial tumors. Late toxicity on the bronchial wall is still too high and was attributed mainly to contact between the catheter and the bronchial mucosa. Exclusive HDR brachytherapy should be restricted to carefully selected patients for whom there is no alternative curative treatment. New bronchial applicators and a lower dose per fraction may reduce the incidence and attenuate the severity of late complications.

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Key words: brachytherapy; endobronchial irradiation; lung cancer; radiotherapy

Abbreviation: HDR=high-dose rate

Endobronchial carcinoma can now be treated by endoluminal brachytherapy due to progress in the miniaturization of the sources of iridium 192 and techniques for remote afterloading of indwelling catheters. Initially tested with low-dose rate sources based on the radiobiology of conventional brachytherapy, endobronchial brachytherapy with high-dose rate (HDR) sources (>10 Gy/h) has now been introduced. This offers the advantage of a short duration of treatment as an outpatient with optimal radioprotection, although it does require dose fractionation over a number of sessions. The rapid decrease of dose radiation is a function of the
distance from the source following an inverse square relationship. This implies a highly restricted target volume encompassing the endobronchial component and ideally the peribronchial areas around the tumor. HDR endobronchial brachytherapy has been successfully employed in the palliative treatment of tumoral bronchial obstruction. It has led to symptomatic improvement in 70 to 80% of cases and objective regression of tumors in two thirds of cases. These results have prompted the use of endobronchial brachytherapy in curative regimens in combination with external radiotherapy aimed at the endobronchial part of the tumor. However, the value of endobronchial brachytherapy under these conditions has yet to be established owing to differences in the published series and difficulties in evaluating the relative influences of the external and endobronchial irradiation.

Endobronchial brachytherapy as a curative treatment for small endobronchial lesions has been tested only in a limited number of patients. We report herein a pilot study evaluating HDR endobronchial brachytherapy as exclusive treatment of patients with localized endobronchial tumors that were judged to be not suitable for other treatments on account of severe respiratory failure or previous treatment for a lung cancer.

**Materials and Methods**

**Patient Selection Criteria**

The patients included in the trial fulfilled the following criteria: (1) histologic evidence of non-small cell lung cancer in a non-radiated tissue accessible to flexible fiberoptic bronchoscopy; (2) endoscopic measurement of the lesion ≤1 cm; (3) exclusive endobronchial development proved by the absence of visibility of the tumor on CT scan; (4) absence of hilar or mediastinal lymph node enlargement >1 cm on CT scan (N0); (5) contraindication of alternative therapy (ie, surgery or curative external radiotherapy) in patients with severe respiratory insufficiency (FEV₁ <0.8 L) or treatment by surgery (lobectomy or pneumonectomy) or external radiotherapy of a previous primary lung cancer; and (6) informed consent. For instance, endobronchial brachytherapy was proposed in patients in whom endoscopic examination had detected a second primary tumor in the remaining lung after pneumonectomy for a previous cancer, or after detection of a small endobronchial tumor in a patient with severe obstructive respiratory disease who could not benefit from surgery or external radiotherapy.

**Technique for Endobronchial Brachytherapy**

The treatment was carried out using an HDR remote after-loading system (Micro-Selectron; Nucletron Oldelft Corp; Columbia, Md) with a high activity source (iridium 192 with initial activity of 10 Ci). Flexible bronchoscopy was performed under local anesthesia in most patients, although some fasted patients were given general anesthesia after premedication, including a corticosteroid (40 mg methylprednisolone IV) and prophylactic antibiotics. The lesion was visualized on a chest radiograph with the flexible bronchoscope positioned at the site of the tumor, under identical conditions to those of the subsequent brachytherapy. A 1.7- or 1.9-mm-diameter catheter (1-mm flexible catheter equipped with an angiographic guide) was then introduced into the operating channel of the flexible bronchoscope and positioned beyond the tumor up to the end of the bronchial tree. The flexible bronchoscope was withdrawn from the catheter, which was then fixed to the nostril of the patients. To cover as much of the tumor lesion as possible, one to three catheters were employed depending on the exact location of the tumor. The final position was checked by a further endoscopic examination.

A metal wire with lead markers every 1 cm was introduced into each applicator to check the stopping positions of the source on orthogonal chest radiographs. The target volume was determined by both the chest physician and radiotherapist on the control radiographs by defining the stopping positions of the source, by comparison with the locating chest radiograph (endoscope in position), including a 2-cm security margin on either side of the lesion. The spatial coordinates of these points were then introduced into a computer planning system (Nucletron Planning System; Nucletron-Oldelft Corp; Columbia, Md) supplied with the source projector to determine the dwell times of the source at each treatment point (source moving in 5-mm steps) in order to optimize dosimetry and avoid “hot” or “cold” spots. The catheters were then connected to the source projector (Micro-Selectron). A dummy source was passed through each catheter before treatment to check for any possible obstruction on subsequent passage of the source. After each treatment session (lasting 5 to 10 min), the catheters were removed in the treatment room.

**Therapeutic Protocol**

In an attempt to assess the tolerance of the bronchial wall to repeated high-dose endoluminal irradiation, and to avoid undue toxicity, the treatment was administered following a dose escalation protocol at weekly intervals in fractions of 7 Gy prescribed at 1 cm from the axis of the source. The first two patients received three fractions of 7 Gy, the next four patients received four fractions of 7 Gy and in the absence of serious immediate toxicity in the bronchial wall, the later patients received five fractions of 7 Gy for a total duration of treatment of 4 weeks (one fraction per week). This protocol has been approved by the Consultative Committee for the Protection of Persons in Biomedical Research of Lyon.

**Evaluation of Response and Follow-up**

The pretreatment workup included the following: bronchial endoscopy and chest CT scan; respiratory function tests with spirometry; and resting arterial gas determinations. The endoscopic evaluation of the response to treatment was carried out 2 months after the end of the treatment, and endoscopic checks were carried out every 3 months for 1 year and then every 6 months. Evidence for local complete response was macroscopic disappearance of the tumoral lesion with negative results of biopsies. Chest CT scan and respiratory function tests were carried out 6 months after treatment.

**Statistical Analysis**

This pilot study of high-dose endobronchial brachytherapy used as sole treatment for small endobronchial tumors was designed to evaluate local control of the neoplasm, disease-free
and overall survival, and immediate and delayed toxicity. Survival was evaluated from the first day of treatment using the method of Kaplan-Meier with the date point fixed at May 15, 1995.

RESULTS

Population

From July 1990 to May 1993, 19 patients were included in the trial. They were all men (mean age, 61.6±13.6 years). The details of the lesions treated are listed in Table 1. The contraindications for surgery or external radiotherapy included respiratory insufficiency with chronic obstructive lung disease (FEV₁ <0.8 L) in five patients, surgical treatment of a previous tumor for 10 patients (pneumonectomy in six) combined with mediastinal irradiation for five of these patients, treatment of a previous tumor by radiotherapy alone in two cases, cardiac failure in one patient, and HIV infection with severe immunodepression in one patient.

Treatment

Two patients had previously been treated before the endobronchial brachytherapy, one by cryotherapy and the other by chemotherapy, without any effect on the endobronchial lesion. Table 2 lists the details of the HDR endobronchial brachytherapy and the allocation of patients to the different dosages. The magnitude of the mean length of tissue treated (6.1±3.4 cm) was accounted for by the 2-cm margin of security on either side of the tumor site. A patient with an epidermoid tumor in three endobronchial sites required insertion of three catheters for the HDR brachytherapy.

![Figure 1. Survival (Kaplan-Meier-plot) from first treatment.](attachment:figure1.png)

Table 1—Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
</tr>
<tr>
<td>Age, yr, SD</td>
<td>61.6±13.6</td>
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<tr>
<td>Karnofsky index, SD</td>
<td>78.4±8.9</td>
</tr>
<tr>
<td>Histologic types</td>
<td></td>
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<tr>
<td>Squamous carcinoma</td>
<td>16</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>1</td>
</tr>
<tr>
<td>Tumor location*</td>
<td></td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate bronchus</td>
<td>1</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>9</td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>5</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>2</td>
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</tbody>
</table>

*One patient was suffering from three independent tumor locations (squamous cell carcinoma).

Local Control of Tumor

Eighteen patients could be evaluated for local control of the tumor 2 months after the end of the treatment. One patient committed suicide 1 month after the last session (macroscopic disappearance of the tumor). Tumor control was not checked histologically in this case. Histologic evidence of disappearance of the tumor was obtained in 15 patients, giving a local control rate of 83% (15/18). One of two patients in group 1 (three fractions of 7 Gy), three of four in group 2 (four fractions of 7 Gy), and 11 of 12 in group 3 (five fractions of 7 Gy) were in complete response 2 months after treatment. One patient (treated with four fractions of 7 Gy) with uncontrolled tumor 2 months after treatment had a surgical resection of the left upper lobe without complication despite the contraindication of cardiac insufficiency for an initial surgical intervention.

Of the 16 patients endoscopically evaluated 1 year after treatment, 12 (75%) exhibited histologic evidence of tumor control. Of these patients in complete response at 2 months, we observed only one local relapse during the follow-up period. No mediastinal or isolated metastatic relapse was detected in these patients.

Survival

With a mean follow-up of 28 months, (range, 7 to 49 months), seven patients were alive with no evi-
idence of disease; 12 had died, two from complications of the treatment, three from intercurrent disease (suicide, pancreatitis, stroke), one from tumor progression, two with a second lung primary tumor, and four of unknown causes. The overall survival rate for these 19 patients was thus 78% at 1 year and 58% at 2 years with a median value of 28 months (Fig 1). The disease-free survival could not be evaluated beyond 1 year as endoscopic examinations were not carried out systematically by the chest physicians in these patients with respiratory insufficiency. The 1-year disease-free survival rate was 70%.

Toxicity

The immediate tolerance of the treatment was satisfactory, with one episode of slight pneumothorax (undrained) and one case of bronchial infection with a favorable outcome out of 87 applications. During treatment, early reactions of mucitis manifested as inflammation of the bronchial mucosa; a few false membranes were noted. None required any specific treatment.

The delayed toxicity was manifested as an asymptomatic partial fibrous stenosis of the treated bronchus in 10 of 18 patients (group 1, one of two; group 2, one of four; group 3, eight of 12) not requiring any particular treatment. The two severe complications were necrosis of the bronchial wall and hemoptysis. Two patients treated with five fractions of 7 Gy developed major necrosis of the bronchial wall with no obvious progression of the tumor. It was seen as a fibrinoid mucosal necrosis around the bronchus, which in some cases was obstructive giving rise to an irritating cough and recurrent infections. These severe necroses occurring 4 and 6 months after treatment did not heal despite prolonged treatment with corticosteroids. One was complicated by fatal hemoptysis. Overall, two patients died of hemoptysis: one died 12 months after treatment with no endoscopic evidence of tumoral relapse 2 months previously (upper left lobe tumor); the second died 18 months after treatment, 1 year after observation of necrosis of the bronchial mucosa (absence of residual tumor on biopsy specimen). This patient had been treated using three catheters for endobronchial brachytherapy for three epidermoid tumors in the right bronchial tree 18 months after removal of the left lung. The rate of major complications was thus three of 18 (16.5%), but may have been underestimated owing to the occurrence of four deaths of undetermined origin.

No deterioration in respiratory function after treatment was observed in the patients with chronic obstructive lung disease nor was there any evidence of radiation fibrosis on CT scan.

Discussion

The endoscopically evidenced tumoral regression after HDR endobronchial brachytherapy in patients treated palliatively for lung cancer prompted use of this technique as a curative treatment in early stages of non-small cell lung cancer. In view of the lack of long-term toxicity data on HDR endobronchial brachytherapy, we selected a population of patients whose tumoral lesions were limited to the bronchial wall and for whom respiratory insufficiency ruled out surgical treatment or external radiotherapy. The limitations of external radiotherapy for patients with respiratory insufficiency are not well established, although the risk of fibrosis related to curative doses of irradiation were judged not acceptable for the patients in the present study (single lung, respiratory insufficiency with FEV1 <0.8 L). The only other therapeutic option would have been chemotherapy, although most of our patients had invasive lesions that were inaccessible to chemotherapy owing to its limited range of action across the bronchial wall. Only four patients with epidermoid carcinoma in situ could have been treated by chemotherapy.

The treatment schedule comprised administration of five fractions of 7 Gy at 1 cm from the source, designed to deliver to the tumor a dose equivalent to 48 Gy (linear quadratic model, α/β=10 Gy) in low-dose rate brachytherapy. The choice of a fraction size of 7 Gy prescribed at 1 cm distance from the source has been based on some reports in which the use of a dose per fraction from 7 to 10 Gy at 1 cm was effective in the treatment of endobronchial carcinoma and associated with an acceptable rate of radiation-induced bronchitis or pulmonary hemorrhage. In the absence of accurate data on the tolerance of the bronchial wall to repeated high-dose irradiation, we decided to employ a dose escalation protocol. The absence of significant early toxic reactions in the patients treated with three and four fractions of 7 Gy prompted us to administer the full dose of five fractions of 7 Gy in the remaining patients without delay.

Endoscopic control of tumor 2 months after treatment demonstrated the ability of HDR brachytherapy to control small-sized tumors (<1 cm diameter) of the bronchial wall. In 15 of the 18 evaluable patients, there was no macroscopic evidence of tumor and results of all biopsies were negative. With a mean follow-up period of 28 months, the observation in these patients with complete response of one case of local relapse and the absence of mediastinal or metastatic neoplasm indicated the efficacy of this local treatment at an early stage of non-small cell lung cancer. These results are in agreement with
those of Trédaniel et al\textsuperscript{12} using a therapeutic protocol of six fractions of 7 Gy at 1 cm from tumors of the bronchial wall (without specification of the maximal diameter). These authors reported a rate of histologic local control of 72\% (Table 3). Our treatment failures may be accounted for by insufficient dosage in one of the patients treated with three fractions of 7 Gy. For the other two patients without control, there may have been an underestimation by endoscopy of the true size of the tumor, especially in the bronchial submucosa. This was confirmed by analysis of a specimen removed on subsequent surgery in one of these patients.

The survival rates are somewhat disappointing in the light of the curative efficacy and the size of the tumors. Apart from the problem of treatment-related complications, analysis of mortality showed a significant number of deaths from nonneoplastic causes in this population of patients with severe respiratory insufficiency. Similar findings were reported by Trédaniel et al\textsuperscript{12} on 29 patients selected on similar criteria (Table 3). Among the 19 patients for whom no satisfactory alternative treatment could be proposed, seven are still in remission, with a 4-year follow up for two patients who were treated for a second lung tumor after pneumonectomy.

The incidence of severe complications (fatal hemoptysis and necrosis of the bronchial wall) of HDR endobronchial brachytherapy varies considerably in the different reports. The rate of fatal hemoptysis ranged from 0\% to 32\%\textsuperscript{6,18} over the various published series. The incidence of hemoptysis appears to be somewhat in excess of that expected from the normal course of lung cancer. Analysis of complications is hampered by several factors: (1) lack of agreement on terminology to describe the toxicity of HDR brachytherapy on the bronchial wall despite the classification proposed by Speiser and Spratling,\textsuperscript{19} which does not include massive necrosis of the bronchial wall source of fistulas and hemorrhage; (2) differences in the patient populations and associated treatments (laser), each with their own toxicities,\textsuperscript{20} and previous external radiotherapy; and (3) the palliative nature of most treatments with the inherent lack of long-term assessment of toxicity. Relative to low-dose rate brachytherapy, the increase in dose rate as in dose per fraction induces a more marked effect on healthy tissues with low cellular turnover than on tumor tissue. This represents a source of latent complications and points to the need for long-term evaluation of toxicity of HDR brachytherapy, as Speiser and Spratling\textsuperscript{19} found that the sole predictive factor for occurrence of radiation bronchitis was duration of survival.

This study produced a good estimate of the late toxicity of HDR endoluminal irradiation on the bronchial wall in the absence of other treatments and in patients who had not received previous radiotherapy. The level of toxicity is high and may have been underestimated in view of the four deaths from undetermined causes. The appearance of fibrous alterations of the irradiated bronchial wall of a partially obstructive nature was commonplace but did not lead to frank symptoms or later complications over a mean follow-up period of 28 months. These bronchial modifications may be viewed as acceptable healing rather than as true complications. However, necrosis of the bronchial wall observed in two patients with a major risk of vascular erosion and fatal hemoptysis, and the death of two patients from hemoptysis, illustrate the potential toxicity of this technique. The factors leading to severe complications, apart from the HDR delivered to the bronchi along with that from prior radiotherapy,\textsuperscript{21} include the length of tissue treated,\textsuperscript{20} which leads to a reduction in normal safety margins, certain localizations (upper lobes, left bronchial stem) due to proximity of pulmonary arterial vessels,\textsuperscript{6} and the fact that the dose is delivered 1 cm from the source irrespective of the diameter of the bronchus to be treated.\textsuperscript{22} Two main factors may have accounted for the serious complications of local radiation therapy: dose per fraction and contact of the catheter with the bronchial mucosa. In view of the fact that the dose rates were close to those of external radiotherapy, a more important fractionation of the total dose should reduce the incidence and attenuate the severity of later complications,\textsuperscript{6} especially for the treatments with curative intent. It would thus be unwise to exceed a 5-Gy fraction at 1 cm from the source in this type of treatment. However, the interest of a large number of fractions appears to be negligible in

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**Table 3—Sole Brachytherapy for Selected Non-small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Treatment (Gy at 1 cm)</th>
<th>Median Follow-up, mo</th>
<th>Histologic Local Control, %</th>
<th>1-yr Survival, %</th>
<th>Major Complications, %</th>
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<tr>
<td>Trédaniel et al\textsuperscript{12}</td>
<td>29</td>
<td>7 Gy×6</td>
<td>23</td>
<td>72 (18/25)</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Current study</td>
<td>19</td>
<td>7 Gy×3 (n=2)</td>
<td>28</td>
<td>83 (15/18)</td>
<td>78</td>
<td>16</td>
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<tr>
<td></td>
<td></td>
<td>7 Gy×4 (n=4)</td>
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<tr>
<td></td>
<td></td>
<td>7 Gy×5 (n=13)</td>
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</table>

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the palliative treatment of obstruction where the limited survival of the patients does not allow evaluation of long-term complications. Long-term toxicity to the bronchial wall may also be prevented by centering the source in the bronchial lumen to avoid close contact between the source and the bronchial wall. Contact between the catheter and bronchial mucosa may well lead to repeated administration of high doses of radiation to the bronchial wall, a probable determinant in later parietal necrosis. The use of centering devices such as a protective sleeve around the vector catheter, and more particularly, the use of a probe with retractable flaps at the level of the trachea and large bronchial trunks improves distribution of the radiation dose and protects the bronchial wall from overdosage. We have not observed any cases of parietal necrosis since using applicators with retractable flaps. Such applicators will allow us to prevent the alterations of the source positions in the treated bronchus from one application to the next one, which probably represents a significant factor of variation in the dose distribution with flexible 1.7-, or 1.9-mm diameter catheters.

HDR endobronchial brachytherapy thus appears to be an effective treatment for small endobronchial tumors in patients whose respiratory insufficiency precludes alternative treatments. The toxicity of the current protocol, however, remains too high for use in patients with small endobronchial tumors who could benefit from surgery or external radiotherapy. The treatment of "roentgenographically occult" endobronchial carcinomas remains a difficult problem, considering the frequent occurrence of synchronous and/or metachronous cancers, and so the need to preserve the pulmonary function. For patients whose pulmonary function allows external-beam radiation, the combination of limited-field external-beam radiotherapy, using possibly three-dimensional conformal radiotherapy, and intraluminal brachytherapy could both increase the delivered dose to the tumor and reduce the pulmonary toxicity of external radiotherapy, as the delayed toxicity of brachytherapy on the bronchial wall. Saito et al treated 49 roentgenographically occult endobronchial carcinomas in 41 patients for whom surgery was medically not indicated, with such a combination of external-beam irradiation (40 GY in 20 fractions) and low-dose rate endobronchial brachytherapy of 25 GY in five fractions (doses were prescribed to a depth depending on the diameter of the treated bronchus, between 3 and 9 mm). Only two patients have had recurrences with a median follow-up of 24.5 months. Radiation pneumonitis was observed for two patients. Neither severe bronchial stenosis nor bleeding occurred during a follow-up period ranging from 1 to 41 months. Nevertheless, exclusive HDR brachytherapy is a less costly treatment for lung parenchyma, which may prove valuable in patients with lung tumors that are liable to spread to other sites. The success of surgery after failure of endobronchial brachytherapy, however, may be compromised by damage to a bronchus subjected to high doses of radiation. Before general use as an alternative to external radiotherapy or surgery, curative intent HDR brachytherapy will probably see developments of high-dose fractionation and improvements in the techniques of application designed to reduce delayed toxicity.

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REFERENCES