Prolonged Survival After High-Dose Rate Endobronchial Radiation for Malignant Airway Obstruction*

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Study objective: To show that prolonged survival can be observed after high-dose rate (HDR) endobronchial brachytherapy as the sole treatment for some selected patients presenting with an endobronchial malignant obstruction.

Patients: Twenty-nine patients (group 1) who presented with an endoluminal localized tumor without metastatic extension were treated by HDR endobronchial brachytherapy and are compared with 22 subjects who presented with extraluminal dissemination and were palliatively treated (group 2).

Treatment protocol: Treatment consisted of sessions of two exposures, delivering 7 Grays at a 10-mm radius from the center of the applicator each, and repeated every 15 days, to a maximum of six exposures. Endoscopic response and survival are the main criteria of assessment.

With an annual incidence of 20,000 cases occurring in France, lung cancer represents our greatest oncologic challenge.1 Metastatic disease is common, pointing to the need for effective systemic therapy,2 as recently emphasized by many reports of experiments with a multimodality approach.3,4 However, endobronchial occlusion is a common and potentially life-threatening complication, not only for patients with recurrent disease, but also at initial diagnosis;5 thereafter, failure to obtain local control continues to be a major issue.6 Patients who develop endobronchial disease often become very symptomatic, with cough, dyspnea, hemoptysis, and obstructive pneumonitis.

In such situations, the primary goal of treatment is to establish or maintain a patent airway, albeit temporarily.7,8 It is important to use a relatively easy-to-perform method, which has minimal complications. External-beam radiotherapy (EBR) is considered to be the established treatment for those who are not candidates for surgery.9,10 Laser photoresection11 and cryotherapy12 can produce dramatic effects, but have some important limitations.

Unlike EBR, high-dose rate (HDR) endobronchial brachytherapy produces much more localized treatment, sparing the surrounding tissues from the early and late effects of radiation.13-15 Until now, it has essentially been used as a palliative treatment,16 though it has occasionally been used for recurrences after surgery and/or radiation. We think that it can also be used as the sole treatment for a few carefully selected patients, with good local results and prolonged survival.

A pilot study to examine the effectiveness of intraluminal irradiation using a remote afterloading system HDR has been in progress in our institution since February 1990. The purpose of this report is to present our results using HDR endobronchial brachytherapy for 29 patients who presented with an endoluminal localized tumor without metastatic extension (group 1), and to compare them with those obtained for 22 subjects palliatively treated (group 2).

Patients and Methods

Patients

From February 1990 to June 1992, 66 patients underwent 295 endobronchial procedures (mean, 4.5 procedures per patient;
Table 1 — Clinical and Therapeutic Characteristics of 51 Patients Who Underwent Endobronchial High-Dose Rate Brachytherapy (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Age, yr (SD)</td>
<td>62.3 (8.3)</td>
<td>64.7 (10.5)</td>
</tr>
<tr>
<td>Karnofsky index (SD)</td>
<td>85.9 (11.5)</td>
<td>72 (13.6)*</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>No. of applications (SD)</td>
<td>5.72 (0.8)</td>
<td>4.7 (1.6)</td>
</tr>
<tr>
<td>Length (cm) of endobronchial tumor</td>
<td>2.5 (1.7)</td>
<td>4.7 (2.7)</td>
</tr>
<tr>
<td>Length (cm) of treated bronchus (SD)</td>
<td>7.8 (4.4)</td>
<td>8.3 (3.8)</td>
</tr>
</tbody>
</table>

*p<0.001.

SD, 1.7; minimum, 1; maximum, 6. Sixty-one were men and 5 were women, ranging in age from 35 to 85 years (mean, 61.5 years; SD, 10.2). Three subjects presented with endobronchial obstruction secondary to chemoresistant Hodgkin’s disease and non-Hodgkin’s lymphomas and are not presented in this study.

Sixty-three patients had primary carcinoma of the tracheobronchial tree. The most common tumor was squamous cell carcinoma, which occurred in 57 patients; 4 patients had adenocarcinoma, 1 had a small cell, and 1 had a large cell tumor. The tumor was located in the left bronchial tree in 26 patients (42 percent), in the right bronchial tree in 23 patients (36 percent) and in the trachea in 14 patients (22 percent). Twelve patients received curative HDR endobronchial brachytherapy as part as a multimodality treatment program, namely as a boost after EBR in the initial therapy of a primary tumor. As the respective effects of HDR and EBR can hardly be distinguished, those patients, although having received curative intent treatment, were excluded from the present analysis.

The remaining 51 patients received HDR endobronchial brachytherapy as their sole treatment, and are the subject of this report (Table 1). We have defined two groups of patients, according to the extension of the disease: group 1, patients presenting only with endobronchial disease; and group 2, composed of patients with extraluminal extension. To be selected for this therapy, patients had to meet the following criteria: histologic evidence of endobronchial visible carcinoma; Karnofsky performance status ≥ 50; to be fit enough to undergo numerous flexible bronchoscopies; informed consent to the procedure; and expected survival of more than 2 months.

Group 1 consisted of 29 patients. For patients to be eligible in this subgroup, the tumor had to be, to all appearances, limited to the bronchial lumen and bronchial wall without adjacent parenchymal and nodal extension, and metastatic disease, as judged by chest, cranial, and upper abdominal computed tomographic (CT) scans, and bone scintigram. All the tumor volume had to be encompassed in the reference isodose. No form of treatment other than HDR brachytherapy was given to these patients. Three patients had recently diagnosed lung carcinoma and were treated because of severe chronic respiratory failure, which excluded the possibility of any other local or systemic therapy; the 26 other subjects were either relapsing from a previously treated tumor or presented what seemed to be a second primary lung cancer.

As an example, the typical situation in this group was represented by subjects previously operated on with pneumonectomy followed by EBR, including the mediastinum, and who were suffering from a contralateral tumor. Among this group, 15 patients had previously been operated on; surgery was the sole treatment in 7 patients, had been followed by EBR in 5 patients, and chemotherapy in 3 patients. Eleven patients had not been operated on and had received EBR as the sole treatment for 6 of them, and in combination with a polychemotherapy protocol in 5 cases. Among the 16 patients who had previously received EBR, the delivered initial dose was above 55 Gy in 11 cases. The median intervals between the first treatment and the present tumor episode was 30 months after surgery, 19 months after EBR, and 15 months after chemotherapy.

Group 2 consisted of 22 patients who presented with an endobronchial tumor with endobronchial extraluminal dissemination (n = 15) or peripheral metastases (n = 7; supraclavicular lymph node metastasis: n = 3; bone metastasis: n = 2; liver metastasis: n = 1; brain metastasis: n = 1). Median Karnofsky index was significantly lower than in group 1 patients, mainly due to the different extension of the disease. Almost all these subjects presented with severe respiratory symptoms, namely hemoptysis, cough, and shortness of breath. Among this group, 8 patients had previously been operated on; surgery was the sole treatment for 4 patients and had been followed by EBR for 4 patients. Fourteen had not been operated on; 1 patient was thus treated because of severe chronic respiratory failure, excluding the opportunity of radical treatment; 1 patient suffered from a small-cell lung cancer, who was relapsing after two protocols of polychemotherapy; 12 patients had received EBR as the sole treatment for 6 of them, and in combination with a polychemotherapy protocol in 6 patients. Among the EBR-treated patients, nine patients had received a dose above 55 Gy. The median intervals between the first treatment and the present tumor episode was 41 months after surgery, 14 months after EBR, and 10 months after chemotherapy. Nine patients had also been treated by laser (n = 4) or cryotherapy (n = 5) before completion of HDR brachytherapy, with a poor symptomatic result.

Clinical assessment of response was noted whenever possible. Bronchoscopic examination with systematic bronchial biopsies were performed 2 months after the end of the procedure. Macroscopic endobronchial aspect had to be noted; a macroscopic complete response (CR) was defined as the total disappearance of endobronchial tumor without any mucosal ulceration or irregularity; histologic CR was defined as the disappearance of malignant cells on systematically performed biopsies; a partial response (PR) was when there was definite, but not complete, tumor regression qualified by the physician as more or less 50 percent regression of the initial tumor burden. Clinical and endoscopic follow-up were then noted (control fiberoptic bronchoscopies with systematic biopsies had to be done every 4 months, if the patient stayed asymptomatic, or earlier in case of symptoms). Thus, endoscopic response and survival are the main criteria of assessment. The minimum of follow-up for patients included in this report is 4 months.

Endobronchial Brachytherapy Technique

An HDR remote afterloading system (Micro-Selectron-HDR, Nuclotron Trading Ltd) was used; it had high activity (10 Ci) iridium-192 sources, which are retained within a tungsten safe in the treatment unit when not in use. The iridium source is attached to a cable that is mechanically driven at high speed in the applicator. It can be installed in an existing radiotherapy facility such as that used for cobalt teletherapy or a linear accelerator.

Fiberoptic bronchoscopy was performed under local anesthesia. A large-channel flexible bronchoscope (Olympus BF type P20D, or Pentax FB 18X) was used to identify the site of the tumor, its endobronchial length whenever possible (ie, when the occlusion was not complete), and its position relative to the carina. A treatment applicator (1.9 mm diameter) was then
passed down the working channel of the bronchoscope and positioned alongside or through the endobronchial tumor under direct vision. A guidewire was inserted into the applicator to facilitate the careful withdrawal of the bronchoscope, leaving the applicator in situ, secured to the nose with tape. The guidewire was then also withdrawn and another metal wire was advanced to the applicator tip. This wire has radiopaque graduations at 1-cm intervals over a total length of 24 cm. Anteroposterior and lateral chest radiographs were taken with this graduated insert in place. The carina was identified on the radiograph and the 1-cm graduations were used to identify the tumor site.

Target volume was defined by the length of bronchus to be treated, the source stopping positions within the applicator, and the distance from the applicator where the reference dose had to be delivered. It was drawn on the localization film, jointly by the chest physician and the radiotherapist. The data were then transferred to the treatment planning software, for calculation of treatment times and dosimetry. The source was programmed to advance in 5-mm steps along the chosen treatment length, and the dwell time in each position was determined by the strength of the source and the prescribed dose.

The patient was then transferred to the brachytherapy theater and the applicator was connected to the treatment unit. All personnel must leave the room during treatment and patients are observed on closed-circuit television. The source can be rapidly withdrawn into the safe in the treatment unit if immediate medical or nursing care is required. At the end of the treatment session, lasting 5 to 10 min, the applicator was disconnected from the treatment unit and manually withdrawn.

Protocol

Our protocol was based on a daily exposure of 7 Gy at 10-mm radius from the center of the applicator. Each treatment session consisted of two exposures that were given on two consecutive days. The sessions were repeated every 15 days, to a maximum of 6 exposures; the maximum duration of treatment is therefore 1.5 months.

For group 1, three brachytherapy sessions (ie, six exposures) were planned. Twenty-six patients received six exposures; one patient received five exposures because of fever and chills after the fifth (he was in complete remission 2 months later); two patients received four exposures: one refused the last session, and the other died suddenly of unexplained cause between the last two sessions.

For group 2, two sessions were made; if a good response was therefore noted, a third session was then programmed. Nine patients received three sessions (ie, 6 exposures); ten received two sessions, and three received only one session because of significant clinical deterioration.

Statistical Analysis

The stopping date for the trial observations was August 1, 1992. Actuarial survival was calculated from the date of the first application to the date of death.

Data were analyzed on personal computer (Macintosh, LC). These results were obtained using the 4D software (4.0.6 V). Statistical comparisons between the two treatment groups used the Student’s t test.

Results

Forty-six patients were available for the histologic analysis at 2 months (Table 2). Two patients (one in each group) had died by that time (an autopsy could not be performed). Three patients of group 1 refused further bronchoscopies.

Relief of Symptoms

The evolution of symptoms could not be assessed with sufficient precision for seven patients who lived a long distance from Paris (three in group 1, four in group 2). Fourteen patients in group 1 did not initially suffer functional symptoms, and they remained asymptomatic. Twenty-one of the 30 remaining subjects (70 percent) achieved complete or partial relief of symptoms. Response for cough and hemoptysis (85 percent) was better than for dyspnea (55 percent).

Endobronchial Assessment of Response

Of the 29 patients in group 1, 25 had endoscopic assessment of response: 21 had macroscopic CR, and with 18 histologic CR was noted. Three PR (two > 50 percent and one < 50 percent) and one local failure were observed. Of the 22 patients palliatively treated (group 2), 6 patients presented macroscopic CR, with 2 having histologic CR. Thirteen PR (8 > 50 percent; 5 < 50 percent) and two local failures were noted.

Among the 18 patients of group 1 who achieved histologic CR, 4 local failures later occurred at 6, 7, 12, and 14 months, respectively.

Survival

The mean overall actuarial survival for patients of group 1 was not achieved after 23 months of follow-up (Fig 1). Median actuarial survival was 5 months in group 2; 17 percent of patients were still alive after 1 year of follow-up.

Tolerance

The immediate tolerance of the procedure was good. The main side effect was temporary pleuritic pain induced in many patients when the applicator was advanced near the pleura; this pain always disappeared with the partial withdrawal of the applicator. However, we did not observe any pneumothorax. Three procedures were immedi-
ately followed by abundant bronchial secretions necessitating a new bronchoscopy for aspiration, without preventing the treatment. Two patients had transient fever with chills, without identification of any bacteria, in the 24 h following the treatment.

Two pulmonary abscesses were observed in the treated lung, respectively, 1 and 2 months after the end of treatment; they were successfully treated with adequate antibiotics.

Five patients (10 percent) died of fatal massive hemoptysis: in May 1991, one patient in group 1 had a second primary lung tumor in the upper right lobe, 16 years after left pneumonectomy (as the sole treatment) for squamous cell carcinoma. He received three sessions of HDR brachytherapy with complete macroscopic and histologic response. The recurrence of cough and bronchorrhea 11 months later allowed the endoscopic discovery of a local relapse. The patient died suddenly 2 days later of a massive hemoptysis, before any new treatment could have been planned. The other four patients had been treated in group 2: three tumors were of squamous cell type, and one was an adenocarcinoma; one tumor was located in the trachea, and three others were in the left bronchial tree (main bronchus: n = 2; lower lobe bronchus: n = 1). One patient presented with bone metastasis; the three others had huge thoracic extension. These four subjects had previously received EBR, with a dose above 55 Gy, 48, 15, 9, and 6 months, respectively, before HDR brachytherapy was performed. None of these patients had received laser therapy or cryotherapy. Three of them had received three sessions of two exposures each of HDR brachytherapy, without obtaining more than a partial macroscopic response. They presented with fatal massive hemoptysis 12, 3, and 2 months, respectively, after the completion of treatment. The last patient received only one session of two exposures; the treatment was stopped because of progressive disease at the time of the second planned session; he died of massive hemoptysis 1 week later. All these patients died at home; autopsies were not performed, and superimposed infection could not be assessed.

Two patients of group 1, previously operated on who had achieved a macroscopic and histologic CR, died of a massive bronchorrhea, 6 and 5 months, respectively, after the completion of treatment. The first subject had presented with a relapse on the bronchial suture 9 months after pneumonectomy (followed by EBR at a dose of 60 Gy) for a squamous cell carcinoma. At the time of relapse, the tumor extended to the carina and the opposite main bronchus. Laser therapy did not improve the respiratory situation, and he received three sessions of two exposures each of HDR brachytherapy, according to the usual protocol. The length of bronchus treated, including the lower part of the trachea, was 7 cm. Five months after the completion of treatment, a radiographic image of abscesses was noted on the pneumonectomy side, although the patient was still asymptomatic. The patient died of acute respiratory failure with massive bronchorrhea. The second patient presented with a similar story: he had relapsed on the bronchial suture 27 months after pneumonectomy, followed by EBR at a dose of 60 Gy. Cryotherapy was unsuccessful. He received six exposures of HDR brachytherapy. The follow-up endoscopies with biopsy specimens showed he had achieved a histologic CR. However, a local relapse with positive biopsy specimen was promptly observed 6 months after the completion of treatment. Like the first patient, this second one died of acute respiratory failure with massive bronchorrhea. We attributed these events to a rupture of bronchial suture, with patent local relapse in the second case. No autopsy was performed.

Finally, seven patients (three in group 1, and four in group 2) developed an endoscopic aspect of radiation bronchitis, occurring within the area of prior intraluminal radiation, 2 to 5 months after treatment, but only one subject was symptomatic. For six patients, it consisted of mild mucosal inflammatory response with swelling, associated in five cases with a thin, whitish membrane not causing significant luminal obstruction. One patient complained of severe cough, and the endoscopic aspect was of a more severe local inflammation, with an increase in the fibrinous membrane; this patient was treated with oral steroid and codeine preparation for cough suppression. Systematic biopsy speci-
mens did not show local tumor recurrence. In all cases, this lesion disappeared in a few weeks. None of these patients presented with other complications, especially fatal hemoptysis.

**DISCUSSION**

The aim of the present study was to determine whether endobronchial HDR brachytherapy may constitute a valuable tool for treatment of patients with small endobronchial tumors. For this purpose, we have compared the outcomes of 29 treated patients presenting with a localized endoluminal carcinoma with those of 22 patients treated palliatively, because of their extrabronchial tumor extension.

The results of this study show that, for some carefully selected patients without evident extrabronchial dissemination, HDR brachytherapy can lead to rates of improvement and survival, at least as good as what is achieved with more conventional treatments.\(^{17-19}\) One must keep in mind that these patients, who have lived long enough to develop a second primary cancer, are part of a select group whose characteristics might explain their apparently long survival. However, such patients are excellent candidates for endobronchial radiation.

Articles have been published recently, reporting studies using HDR endobronchial brachytherapy alone or as the main treatment of patients. Burt et al\(^1\) treated 50 patients with inoperable, symptomatic endobronchial carcinoma by a single exposure of intraluminal brachytherapy, delivering 15 to 20 Gy at a 10-mm radius from the center of the applicator, and achieved a good symptomatic response. Mehta et al\(^1\) delivered 4 Gy × 4 fractions over 2 days at 2 cm from source center to 31 patients, achieving a median survival of 4 months. Twenty-four patients with endobronchial tumors that had recurred after EBR were treated by Gauwitz et al\(^2\) with HDR intraluminal irradiation; two sessions were planned, delivering 15 Gy at each treatment; median overall survival was 32 weeks. Bedwinek et al\(^3\) treated 38 patients by three fractions of 6 Grays at a radius of 1 cm from the center of the source, each fraction separated by a 1-week interval; the median survival from the end of the first brachytherapy course was 6.5 months; however, 12 patients (32 percent) died of massive hemoptysis occurring 2 to 56 months (median: 10 weeks) after brachytherapy. Finally, Speiser and Spratling\(^4\) reported their results for 342 patients consecutively treated according to three successive protocols: group 1 patients were treated with medium dose rate and received 1,000 cGy at 5-mm depth for three fractions (\(n = 47\)). Group 2 patients were treated with HDR, 1,000 cGy to a 10-mm depth for three fractions (\(n = 144\)), and group 3 received 750 cGy delivered to a 10-mm depth for three fractions (\(n = 151\)). Each group was divided into curative, palliative, and recurrent categories. Survival from first brachytherapy treatment was, respectively, 9.5 months for curative, 5.6 months for palliative, and 6.2 months for recurrent. Fatal hemoptysis occurred in 7 percent, and radiation bronchitis occurred in 11 percent.

We observed fatal pulmonary hemorrhages in five patients (10 percent); four of these patients had previously received external irradiation with a dose above 55 Gy; moreover, all of them presented endobronchial evidence of local recurrence at the time of death. Table 3 presents rates of this entity, published in the literature, from 1 to 50 percent. It is difficult to separate the relative contribution of treatment and local recurrence to this fatal complication. The question remains whether hemoptysis in these cases is the result of too much treatment or, on the contrary, insufficient treatment allowing the disease to progress. Further data are still needed to explain and, if possible, prevent these fatalities.

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Protocol</th>
<th>% Fatal Hemoptysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt et al(^1)</td>
<td>1990</td>
<td>50</td>
<td>15-20 Gy at 10 mm × 1</td>
<td>1.0</td>
</tr>
<tr>
<td>Khanavkar et al(^7)</td>
<td>1991</td>
<td>12</td>
<td>8 Gy at 5 mm × 2-8</td>
<td>50.0</td>
</tr>
<tr>
<td>Mehta et al(^1)</td>
<td>1992</td>
<td>31</td>
<td>4 Gy at 20 mm × 4</td>
<td>3.2</td>
</tr>
<tr>
<td>Gauwitz et al(^2)</td>
<td>1992</td>
<td>24</td>
<td>15 Gy at 6 mm × 2</td>
<td>4.2</td>
</tr>
<tr>
<td>Bedwinek et al(^3)</td>
<td>1992</td>
<td>38</td>
<td>6 Gy at 10 mm × 3</td>
<td>31.6</td>
</tr>
<tr>
<td>Sutedja et al(^4)</td>
<td>1992</td>
<td>31</td>
<td>10 Gy at 10 mm × 3</td>
<td>32.2</td>
</tr>
<tr>
<td>Aygun et al(^5)</td>
<td>1992</td>
<td>62</td>
<td>5 Gy at 10 mm × 3-5</td>
<td>15.0</td>
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<tr>
<td>Speiser and Spratling(^4)</td>
<td>1993</td>
<td>342</td>
<td>· MDR*: 10 Gy at 5 mm × 3 ((n = 47))</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· HDR: 10 Gy at 10 mm × 3 ((n = 144))</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>· HDR: 7.5 Gy at 10 mm × 3 ((n = 151))</td>
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</table>

\(^{*}\)MDR = medium-dose rate.

**Table 3 — Survey of Literature on Fatal Hemoptysis in Patients Treated by Endobronchial High-Dose Rate Brachytherapy**
recently recommended, all doses should be specified at 1.0 cm from the axis of the catheter and be comprised of an “envelope” or “sleeve” with uniform radius.

Endoscopic aspects of radiation bronchitis occurred in seven patients (14 percent), but were of mild degree, and disappeared after a brief delay. According to the classification recently published by Speiser and Spratling, they would have been classified as grade 1 (six patients) and 2 (one patient). These authors observed a rate of 13 percent for patients of their group 3, receiving treatment similar to ours (750 cGy at a 10-mm depth for three fractions). However, our follow-up is shorter than theirs, and it is possible that we observed new cases.

Our study has confirmed that effective remission of endobronchial tumors can be achieved with HDR endobronchial brachytherapy used as the sole treatment. The duration of response and the survival pattern appear to be similar to those reported with conventional treatment. These benefits are achieved with a less expensive outpatient basis protocol, and without major complications, according to the poor spontaneous prognosis of these patients.

References