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**CLINICAL INVESTIGATION** **Lung**

# HIGH-DOSE-RATE ENDOBRONCHIAL BRACHYTHERAPY EFFECTIVELY PALLIATES SYMPTOMS DUE TO AIRWAY TUMORS: THE 10-YEAR M. D. ANDERSON CANCER CENTER EXPERIENCE

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**Purpose: To evaluate the toxicity and efficacy of Iridium-192 high-dose-rate (HDR) endobronchial brachytherapy (EBBT) for the palliation of symptoms caused by relapsed or persistent endobronchial tumors.**

**Methods and Materials: We reviewed the treatment outcomes between 1988 and 1997 in 175 lung cancer patients who underwent HDR EBBT for recurrent or metastatic tumors at The University of Texas M. D. Anderson Cancer Center. One hundred sixty of these patients had previously received thoracic external-beam irradiation. This updated report includes 74 patients from a previous series. Most patients received 3,000-cGy EBBT delivered at a distance of 6 mm and divided into 2 fractions over 2 weeks. Subjective response was assessed by questionnaire at follow-up. Objective response was assessed by physical examination, bronchoscopy, and chest radiograph.**

**Results: The median actuarial survival for the entire group was 6 months from the time of the first EBBT treatment session. Of the 115 patients (66%) who showed symptomatic improvement, 32% were much improved and 34% were slightly improved. Patients showing improvement survived for significantly longer than those who showed no change or worsening symptoms (7 vs. 4 months, $p = 0.0032$). Repeat bronchoscopy demonstrated a 78% overall objective response rate that correlated significantly with subjective response and symptom relief. Complications occurred in 19 patients (11% crude rate) with an actuarial complication rate of 13% at 1 year from the time of the first EBBT treatment session. The actuarial hazard for fatal hemoptysis due to EBBT was 5%.**

**Conclusion: HDR EBBT effectively palliates most patients' symptoms caused by endobronchial lesions. This relief correlates significantly with an overall survival benefit. Treatment complications appear to be few, even for patients who have received prior external-beam irradiation.** **© 2000 Elsevier Science Inc.**

**Endobronchial radiation, High-dose-rate, Lung cancer, Brachytherapy.**

## INTRODUCTION

The potential to use radioactive sources in or near airway tumors has long been recognized. For example, reports from as early as 1922 describe the implantation of radon seeds in a pulmonary lesion via a rigid bronchoscope (1). Unfortunately, these initial attempts were limited by the fact that physicians and personnel were exposed to high levels of radiation, dosimetry was nonuniform, and tumor access was restricted. With the development of more advanced techniques, such as flexible fiberoptic bronchoscopy and the remote afterloading of high-activity sources, endobronchial brachytherapy (EBBT) has now emerged as a safe and effective treatment (2).

The majority of lung cancer patients are diagnosed with clinically advanced disease. These are tumors that have invaded local tissues or spread to regional lymph nodes, which makes them either inoperable or unlikely to be eradicated by surgical resection alone. The patients, who then undergo combined chemotherapy and radiotherapy or radiotherapy alone, are at substantial risk for intrathoracic relapse or metastasis. Indeed, clinical relapse rates of 30–50% have been noted in prospective trials (3). When local tumor control was defined by the pathological complete response, a rate of 17% has been reported (4). Retreatment options in these patients are often limited because the doses prescribed for definitive external-beam radiotherapy usually preclude the administration of additional external radiation due to the increased risk of severe toxicity to other organs such as the heart or to structures such as the esophagus and spinal cord.

An advantage of EBBT in patients with airway tumors is

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that it allows the delivery of a potentially tumoricidal radiation dose to the site of recurrent disease with less overall risk of substantial injury to the surrounding organs and tissues. An additional particular strength of EBBT lies in its ability to relieve debilitating symptoms, such as dyspnea and hemoptysis. EBBT may also alleviate postobstructive pneumonitis, thereby enabling patients to receive chemotherapy without increased risk of neutropenic sepsis.

At The University of Texas M. D. Anderson Cancer Center, high-dose-rate (HDR), remote-afterloaded, Iridium-192 EBBT has been applied over the past 10 years to palliate patients' symptoms from recurrent or metastatic endobronchial tumors. In this review, we report on this therapy's efficacy and toxicity in a series of 175 consecutive patients with lung carcinoma treated during this past decade at our institution.

## METHODS AND MATERIALS

One hundred ninety-eight consecutive patients who underwent palliative (EBBT) HDR for endobronchial tumors at M.D. Anderson between November 1988 and December 1997 were identified from a Division of Radiation Oncology database. Twenty-three of these patients received treatment for nonpulmonary primary tumors and were excluded from the analysis. The remaining 175 patients included 74 patients who were included in a previous report (5). Patients' hospital and radiotherapy charts were reviewed to determine age, sex, tumor histology, site of bronchial disease, nature of previous or concurrent radiation and/or laser treatment, pretreatment symptoms and performance status, number of EBBT applications, and EBBT dosimetry.

To be eligible to undergo HDR EBBT, patients had to be able to tolerate bronchoscopy, have no bleeding disorder, and have a sufficiently long life expectancy to benefit from palliative treatment. Specific indications for the procedure were a significant, symptomatic endotracheal or endobronchial tumor, inability to undergo tumor resection, or the previous receipt of external-beam radiotherapy in a dose that precluded further similar treatment because of the cumulative risk of significant morbidity.

Each patient underwent a complete history taking and physical examination as well as pretreatment evaluation of their symptoms and determination of their Karnofsky performance score (KPS) (6). Hematology studies were done to determine whether patients had adequate cell counts and to rule out the presence of any bleeding diathesis. In addition to chest radiography, patients underwent flexible fiberoptic bronchoscopy to visualize directly the tumor prior to brachytherapy catheter placement. Only those tumors with an endoluminal obstructive component, not strictly extrabronchial tumors causing extrinsic airway compression, were considered suitable for EBBT. Tumor characteristics such as site, volume, and degree of tracheal or bronchial occlusion were also assessed and documented. Photographs of the tumor were taken through the bronchoscope to allow comparison with post-treatment findings. Some patients with complete airway obstruction underwent neodymium: yttrium-aluminum garnet (Nd:YAG) laser tumor ablation prior to EBBT. A small number of patients received an infusion of paclitaxel as a radiation sensitizer before EBBT as part of a pilot clinical trial (7).

Patients were given intravenous sedation for the bronchoscopy and subsequent EBBT. Continuous pulse oximetry and periodic blood pressure measurements were performed to monitor the patient's status during the procedure. Bronchoscopy was performed transnasally rather than transorally because it ensured greater catheter stability with less likelihood of displacement resulting from patient discomfort or cough.

After evaluating the tumor bronchoscopically, a 6-French flexible nylon catheter was introduced through the working channel of the bronchoscope into the airway lumen. The catheter tip was positioned at least 4 cm beyond to the visible tumor. This localization secured the tip from displacement by lodging it in the bronchiole. Two catheters were sometimes used to achieve adequate dosimetric coverage in patients with more than one disease site. Once the catheter was secured in place with adhesive tape on the patient's nose, a radiopaque "dummy" wire was inserted for fluoroscopic verification of the catheter position. The patient was then transferred to the radiotherapy department, where orthogonal radiographs were obtained for dosimetric planning.

To perform EBBT, the catheter was attached to the Microselectron HDR remote afterloading unit (Nucletron Corporation, Columbia, MD) that contains the Iridium-192 radioactive source. When installed, this source has an active length of 3.5 mm, an active diameter of 0.6 mm, and an initial activity of 10 Ci (370 Gbq). The radioactivity has a half-life of 74 days, which necessitates source replacement approximately every 3 months. The source is attached to a stainless steel cable, which allows it to be moved by 5-mm increments, or "dwell positions," along a 24-cm path, which are modeled by the treatment-planning software.

Using the information from the dummy source wires on the orthogonal films, the total number of dwell positions and source time at each interval were determined to achieve the desired dose to the target volume. A dose of 15 Gy per EBBT procedure at a distance of 6 mm was prescribed for endobronchial tumors and at a distance of 7.5 mm for endotracheal lesions.

Brachytherapy was performed after the physician reviewed and approved the treatment plan, with a repeat procedure scheduled for 2 weeks later. Not all patients went on to have a second EBBT application, either because of disease progression and clinical deterioration or, less frequently, because of complete response to the first treatment. A small number of patients received a third treatment for recurrent or persistent symptoms. One patient received a total of four EBBT applications.

Patients' subjective response to therapy was assessed with a questionnaire at follow-up visits. Repeat physical examination, bronchoscopy, and chest radiography, usually

Table 1. Summary of patient characteristics

| Patient characteristics | *n* (%) |
|---|---|
| Sex | |
| Female | 119 (68) |
| Male | 56 (32) |
| Age (years) | |
| Mean | 60 |
| Range | 28–79 |
| Histology | |
| Squamous cell carcinoma | 90 (51) |
| Adenocarcinoma | 39 (22) |
| Non-small cell carcinoma (NOS) | 29 (17) |
| Smal cell carcinoma | 8 (5) |
| Large/Giant cell carcinoma | 4 (2) |
| Carcinoid/other | 5 (3) |
| Symptoms | |
| Cough | 133 (76) |
| Dyspnea | 149 (85) |
| Hemoptysis | 60 (34) |
| Wheezing | 47 (27) |
| Other | 16 (9) |

done within 2 weeks of therapy, were done to evaluate objective responses. Therapy-related complications were identified at regular follow-up visits at M. D. Anderson or with referring oncologists.

The Kaplan-Meier method was used to determine actuarial survival and duration of symptomatic relief from the time of the first brachytherapy treatment (8). The Pearson Chi-square test was used to evaluate the independence of rows and columns in two-way tables (9). Comparisons between different patient groups were done using the Wilcoxon-Gehan statistical test (10, 11).

## RESULTS

The patients ranged in age from 28 to 79 years (median 60); 119 were men and 56 were women (Table 1). The median KPS before treatment was 70, with the score ranging from 50 to 100. One hundred forty-nine patients (85%) had dyspnea, while 133 (76%) had cough, and 60 (34%) had hemoptysis. Forty-seven patients (27%) reported wheezing prior to EBBT. Sixteen patients (9%) reported other symptoms, such as dysphagia, chest pain, and hoarseness. Non-small cell lung carcinoma was the prevalent histologic type, with squamous cell carcinoma the most common subtype (90 cases, 51%). Other histologic types, in descending order of frequency, were: adenocarcinoma, 39 cases (22%); non-small cell (not otherwise specified), 29 cases (17%); small cell, 8 cases (5%); large or giant cell, 4 cases (2%); and carcinoid or other, 5 cases (3%).

As stated earlier, all tumors had an intraluminal component; however, lesions were predominately on the right side (55%). Nine percent of the lesions had a tracheal component, whereas 40% involved either the right or left mainstem bronchus. The lobar bronchi were involved in 66% of the patients, with an approximately equivalent frequency of lesions in each lobe. Carinal lesions were seen in less than 2% of patients.

The majority of patients (115, 66%) underwent two EBBT applications; 45 patients (26%) underwent only one. Fifteen patients (9%) received a total of three applications. For most of the applications, a dose of 15 Gy was given at a distance of 6 mm; therefore, the most common total doses were multiples of this single dose, or 15 Gy (23%), 30 Gy (58%), and 45 Gy (7%). However, the total cumulative doses actually ranged from 5 to 60 Gy. Twenty patients also underwent Nd:YAG laser tumor ablation either before or concomitant with EBBT. Seventeen patients received a 24-h infusion of paclitaxel before their EBBT session.

One hundred fifteen patients showed symptomatic improvement. Of these, 56 (32%) showed considerable improvement, while 59 (34%) showed only slight improvement. Only a minority had no relief (29 patients, 17%) or a worsening of symptoms (18 patients, 10%). Thirteen patients did not return for additional assessment or treatment. The mean duration of response was 3.8 months. This symptom relief correlated with a longer overall survival (see below).

Most of the patients undergoing repeat bronchoscopy demonstrated a response that was complete in 14 patients (12%) and partial (defined as at least 50% of normal lumen reopened) in 76 patients (66%), corresponding with an overall 78% objective response rate. Twenty-three patients were assessed as having no response (20%) and 2 patients had disease progression (2%). There was a significant association between the patient's subjective assessment of treatment response and objective findings from repeat bronchoscopy ($p = 0.024$); however, no association was seen between symptom relief and increased aeration on follow-up chest films. Radiographic appearance was improved or stable in 136 patients (88% of those with additional imaging). Only 18 patients (12%) were felt to have a worsened chest film.

At the time of analysis, 32 patients were alive as of the last follow-up visit. Overall actuarial survival for the entire cohort from the time of the first EBBT session was a mean of 6 months, ranging from 0 to 54 months. Actuarial survival was significantly longer in the responsive patient group than in those who did not respond favorably (7 vs. 4 months, $p = 0.0032$) (Fig. 1). Prebrachytherapy cough was significantly associated with worse survival ($p = 0.05$); however, such a relationship was not seen for other symptoms. However, no meaningful difference in pretreatment characteristics was found between patients who responded favorably to EBBT and those who did not.

Relatively few patients showed treatment-related complications (19 of 175, with a crude rate of 11%). The actuarial risk of any complication was 13% at 1 year from the time of the first EBBT application. Eight patients died from massive hemoptysis after EBBT, corresponding to an actuarial rate of bleeding from any cause of 9% at 1 year after therapy. All of these patients' charts were

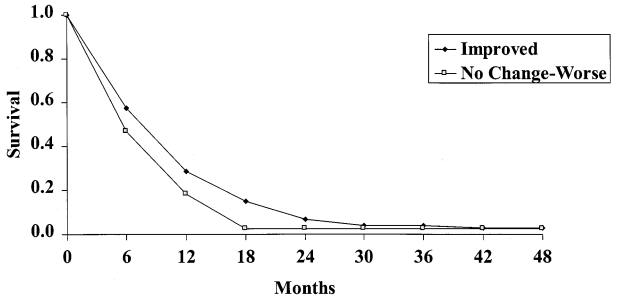


Fig. 1. A comparison of overall actuarial survival from the time of first EBBT by palliative response ($p = 0.0032$).

carefully reviewed to determine whether the cause of bleeding was EBBT or tumor progression and invasion into a major blood vessel. Only 3 patients were determined to have bled as a direct result of EBBT, for an actuarial hazard rate of 2% at 6 months after treatment, which then reached a plateau at 5% at 14 months after treatment. Four other patients had documented gross residual or recurrent bronchial disease at their last follow-up visit and were deemed to have died from local tumor progression. The remaining patient died from pulmonary artery laceration during follow-up bronchoscopy at another institution. Two other fatal treatment-related complications were seen: 1 case of necrosis and fistula formation and 1 case of stenosis and necrosis. Nine other patients experienced post-EBBT sequelae, including pneumothorax (4 patients), nonfatal hemoptysis (2 patients), necrosis (2 patients), and esophageal stricture (1 patient). The actuarial hazard rates for these complications were all less than 5% at 1 year.

## DISCUSSION

HDR EBBT provides prompt relief of symptoms in patients with intraluminal airway tumors. Although external-beam radiation therapy could also be used for this purpose, often it cannot be used because patients have already received definitive irradiation, where additional dose to normal intrathoracic tissues and organs would risk severe and debilitating chronic complications. For patients who have not had prior thoracic radiation therapy, a combination of external-beam and endobronchial radiation therapy can alleviate symptoms. Indeed, the two modalities together have been shown in a randomized, prospective trial to provide local control superior to that provided by external-beam irradiation alone in the definitive therapy for lung carcinoma (12). However, a recent attempt to compare the two modalities for palliation in a prospective, randomized trial was unsuccessful due to poor patient accrual (13). In another series of patients who received palliative external-beam radiation therapy (14), 41% of patients treated with either 30 Gy over 2 weeks or 20 Gy over 1 week had symptomatic improvement, which is a lower response rate than one might expect from a similar dose of radiation given by EBBT. External-beam radiotherapy may, however, be particularly beneficial for patients who have a tumor component causing extrinsic airway compression, because this type of obstruction is unlikely to be relieved by EBBT alone.

The benefit from HDR EBBT does not appear to be limited to palliation. In particular, the actuarial survival in our patients reporting symptomatic improvement was associated with a statistically significant prolongation of survival 7 months versus 4 months in those who did not report improvement. This finding corresponds with the survival benefit observed by Tredaniel *et al.* (15) in patients treated with HDR EBBT alone for localized endoluminal tumors, although most of the previously untreated patients in that series received six HDR exposures given over three brachytherapy sessions.

Remotely-loaded HDR therapy has been utilized at M. D. Anderson for a variety of reasons. First, the treatment time is much less than that needed for low-dose-rate (LDR) therapy, thus minimizing patient discomfort and eliminating the expense of overnight hospitalization. Second, catheter displacement resulting from patient coughing or movement is much less likely during the short treatment duration. Third, radiation exposure to staff is reduced because the HDR source is remotely afterloaded. Theoretically, there may be a radiobiologic advantage of LDR over HDR therapy in terms of normal tissue tolerance and of less risk for late complications; however, a difference in the clinical response between LDR and HDR palliative therapy has not been shown.

Similar rates of symptomatic relief have been cited in published reports of both LDR and HDR treatment. For example, Raju *et al.* (16) reported on a series of 39 patients treated with afterloaded LDR Iridium-192 that delivered 20 Gy at 1 cm over 60 h, which relieved symptoms in 79–89% of patients. Speiser and Spratling (17) observed symptomatic response rates of 85–99% in 342 patients receiving a range of HDR protocols, often in combination with external irradiation, tailored to therapeutic intent. Similarly, Gustafson *et al.* (18) noted significant clinical improvement in 74% of 38 symptomatic patients treated to 21 Gy at 1 cm given in 3 HDR applications over 3 weeks. Nori *et al.* (19) reported palliation rates ranging from 84% to 100% in 15 patients receiving 12–16 Gy at 1 cm delivered in 3–4 HDR treatments given over 1 month. In the Bedwinek *et al.* (20) series, 76% of the patients had symptomatic improvement in response to a dose of 18 Gy given at a distance of 1 cm in 3 HDR EBBT sessions with 1-week intervals between fractions.

In the series of patients reported on here, an average dose of 15 Gy was administered per application at 6–7.5 mm from the treatment source. Other investigators have used a range of prescription points and fractional doses, which may make direct comparisons between series difficult. For example, a dosimetric analysis of our treatment plans shows that 15 Gy at a 6-mm depth delivers

Table 2. Comparison of fatal hemoptysis complication rates

| Reference | Patients (*n*) | Protocol Dose/Depth/Rx #* | EBXRT† Patient (*n*) | Fatal hemoptysis (%) |
|---|---|---|---|---|
| Miller & Phillips (21) | 88 | 10 Gy/10 mm/3 Rx | Not stated | 0 |
| Aygun *et al*. (22) | 62 | 5 Gy/10 mm/3–5 Rx | 62 | 15.0 |
| Bedwinek *et al*. (20) | 38 | 6 Gy/10 mm/3 Rx | 38 | 32.0 |
| Mehta *et al*. (23) | 31 | 4 Gy/20 mm/4 Rx | 9 | 3.0 |
| Sutedja *et al*. (24) | 31 | 10 Gy/10 mm/3 Rx | 31 | 32.0 |
| Nori *et al*. (19) | 32 | 4–5 Gy/10 mm/3–4 Rx | 32 | 0 |
| Speiser & | 144 | 10 Gy/10 mm/3 Rx | 156 | 7.0 |
| Spratling (17) | 151 | 7–5 Gy/10 mm/3 Rx | | |
| Chang *et al*. (25) | 76 | 7 Gy/10 mm/3 Rx | 59 | 4.0 |
| Gollins *et al*. (26) | 406 | 15–20 Gy/10 mm/1 Rx | 82 | 7.9 |
| Gustafson *et al*. (18) | 46 | 7 Gy/10 mm/3 Rx | 12 | 7.0 |
| Hennequin *et al*. (27) | 149 | 7 Gy/5–15 mm/4–6 Rx | 112 | 7.4 |
| Huber *et al*. (12) | 56 | 4.8 Gy/10 mm/2 Rx | 56 | 18.9 |
| Tredaniel *et al*. (15) | 51 | 7 Gy/10 mm/1–6 Rx | 32 | 10.0 |
| Ornadel *et al*. 928) | 117 | 15 Gy/10 mm/1 Rx | 92 | 11.0 |
| Taulelle *et al*. 929) | 189 | 8–10 Gy/10 mm/3–4 Rx | 117 | 7.0 |
| Present series | 175 | 15 Gy/6–7.5 mm/1–4 Rx | 160 | 5.0 |

* Dose per brachytherapy application/prescription point/number of applications.
† Previous or concurrent external beam irradiation.

8.41 Gy at 1 cm from the radioactive source, and this dose is somewhat higher than the doses given at other centers.

The complication rate in our series compares favorably with those reported from other institutions. Overall, fatal complications were few, even in patients who had previously undergone high-dose external-beam radiation therapy. Pulmonary hemorrhage was the most common fatal complication; however, the risk of this particular complication ranges widely in published reports (Table 2). It is not possible to do a straightforward comparison of complication rates between different published series because some report crude complication rates rather than actuarial complication rates, which are preferable because only patients who are alive and at risk for late sequelae are included. We have reported both rates here to emphasize the fact that the crude complications rate likely underestimates the true proportion.

Other series, particularly that of Bedwinek *et al*. (20), suggested a correlation between the treatment of tumors in the left upper lobe airway and the risk of fatal hemoptysis. One factor possibly contributing to this finding is that the dose was calculated for a linear source path and not modified for curvature within the bronchus. However, our analysis found no correlation between tumor location and risk of complication. Likewise, we observed no association between the number of EBBT applications and the toxicity observed.

This 10-year review of our experience with HDR EBBT at M. D. Anderson demonstrates not only the therapy's efficacy in relieving obstructive airway symptoms, but also the low morbidity associated with the treatment. Most patients respond to therapy and enjoy a survival benefit. The effectiveness of HDR EBBT in combination with chemotherapy or with definitive external-beam therapy to deliver a boost dose remains under investigation.

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