Local Determinants of Response to Endobronchial High-Dose Rate Brachytherapy in Bronchogenic Carcinoma*

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Study objective: **We evaluated bronchoscopic tumor appearance and tumor location as determinants of response to high-dose rate brachytherapy (HDR-BT) in patients with symptomatic unresectable bronchogenic carcinoma previously treated with external-beam irradiation.**
Patients and methods: **Thirty patients with symptomatic endobronchial bronchogenic carcinoma who had previously completed external irradiation were divided into two groups based on whether the initial bronchoscopic appearance showed an endoluminal mass or submucosal infiltration/extrinsic compression. Furthermore, patients were also classified based on tumor location: central (trachea or mainstem bronchi) and peripheral (lobar or segmental bronchi). Patients underwent three treatments of 800 cGy intraluminal irradiation at 2-week intervals, with follow-up evaluation 4 weeks later. We evaluated response in tumor extent based on bronchoscopic and chest radiograph appearance, as well as symptoms with standardized scales.**
Results: **Fifteen of 24 patients who underwent follow-up bronchoscopy had reductions in the degree of endobronchial obstruction. Seven of 24 patients had radiographic improvement in the extent of atelectasis. Patients with both tumor appearances (endoluminal and submucosal/extrinsic compression) had significant improvements following HDR-BT with regard to hemoptysis. Patients with submucosal disease also had improvement in cough. Patients with peripheral tumors had better rates of response for hemoptysis and cough than did those with central tumors.**
Conclusion: **HDR-BT may result in symptomatic improvement in patients with bronchogenic carcinoma, whether characterized endoscopically as endoluminal projection or submucosal infiltration/extrinsic compression. Peripheral tumors have better rates of response than central tumors, possibly on the basis of less extensive disease.** ***(CHEST 1997; 112:946-53)***

Key words: brachytherapy; bronchogenic carcinoma; lung cancer; radiotherapy

Abbreviations: CXR=chest radiograph; ECOG=Eastern Cooperative Oncology Group; HDR-BT=high-dose rate brachytherapy

Lung cancer is the leading cause of cancer death in North America. Of the estimated 170,000 new cases diagnosed each year, up to 80% will be inoperable either at presentation or at thoracotomy.[1] Half of patients with inoperable lung cancer will develop symptoms referable to endobronchial disease,[2] including hemoptysis, cough, dyspnea, and postobstructive pneumonia. External-beam radiotherapy is the standard palliative treatment for patients with inoperable lung cancer. However, up to 40% of patients treated with external-beam radiotherapy will develop recurrent or progressive intrathoracic disease.[3]

High-dose rate remote afterloading endobronchial irradiation (brachytherapy) has been used increasingly as a palliative therapy to improve local control of endobronchial tumor. Studies have reported improved symptoms using high-dose rate brachytherapy (HDR-BT) as the sole treatment modality, or in combination with external irradiation or laser debulking.[4-6] HDR-BT has also been shown to be helpful in the control of symptoms following dose-limiting external irradiation.[7-9]

As a palliative measure, HDR-BT is relatively invasive since in most protocols, multiple bronchoscopies are required for the placement of brachytherapy catheters on successive occasions. Furthermore,

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there is the potential for morbidity and mortality during the placement of the brachytherapy catheters or as a result of the treatment itself. Therefore, there is a need to identify at the outset the patients most likely to benefit from this intervention. To our knowledge, this information is not currently available in the literature.

Radiation delivered by HDR-BT is characterized by a rapid fall-off of radiation from the source originating in the airway.[10] This allows for high doses of radiation to be delivered to target tissues while sparing normal surrounding tissue.[11] Since HDR-BT delivers the highest dose of radiation closest to the source, we hypothesized that endobronchial disease characterized morphologically by submucosal infiltration and/or extrinsic compression may be less responsive than endoluminal disease because of the greater distance from the radiation source. Secondly, we hypothesized that tumors located in the more central airways (trachea or mainstem bronchi) may cause more symptoms than peripherally located disease since there is potentially a greater amount of lung tissue affected, and consequently these patients may respond better to the intervention. Therefore, the purpose of this study was to evaluate the potential importance of bronchoscopic tumor appearance and tumor location as determinants of short-term response to HDR-BT using standardized symptom scores, bronchoscopic appearance, and radiographic change as outcomes.

Materials and Methods

Study Population

All patients referred for HDR-BT to the Radiation Oncology Division at the Royal Victoria Hospital between November 1992 and October 1995 were recruited for the study if they met the following criteria: (1) histologically proven bronchogenic carcinoma; (2) tumor inoperable due to pulmonary function or unresectable due to tumor stage; (3) recurrent or persistent symptoms (hemoptysis, cough, dyspnea, or postobstructive pneumonia) following previous maximal external-beam radiotherapy as determined by the referring radio-oncologist; (4) evidence of endobronchial disease at bronchoscopy; and (5) consent to entry into the study.

Study Groups

Based on the initial bronchoscopy, patients were divided into two groups (Fig 1): group 1, tumor characterized by endoluminal disease, and group 2, submucosal infiltration and/or extrinsic compression, based on a classification system proposed by Buccheri et al.[12] Endoluminal disease was defined as an endobronchial mass presenting as either an irregular cauliflower-like vegetation or as a lobulated fleshy growth. Submucosal infiltration referred to a tumor with an irregular area of mucosal surface that appeared swollen and was surrounded by a halo of redness and engorgement of blood vessels. Extrinsic compression included any form of deformation or narrowing of bronchi, associated with fixity and reduced mobility.

Patients were also classified according to tumor location, either central (originating in the trachea or mainstem bronchi) or more peripheral (originating in lobar or segmental bronchi without abnormalities in the trachea or mainstem bronchi).

Brachytherapy Protocol

All treatments were delivered on an outpatient basis. Patients underwent flexible fiberoptic bronchoscopy following topical anesthesia with aerosolized lidocaine (8 puffs of 10% solution by metered dose unit). Patients were given IV sedation with 1 to 5 mg of midazolam, as well as atropine, 0.6 mg subcutaneously, prior to the procedure.

Endobronchial tumor was identified, and a hollow closed ended 6F polyurethane afterloading catheter (Nucletron; Leersum, Netherlands) was inserted through the biopsy channel of the fiberoptic bronchoscope. The catheter was advanced under direct vision and placed either beyond the obstructing mass or adjacent to it. The bronchoscope was then removed over the catheter and a dummy source with radio-opaque markings at 1-cm intervals was inserted through the treatment catheter. This procedure was repeated if catheters were placed in multiple locations to treat multiple foci of tumor or to irradiate a larger volume of tissue for disease located at a carina. The position of the catheter(s) was confirmed with fluoroscopy in two planes.

Based on knowledge of airway anatomy and tumor location, a treatment plan was generated with custom dosimetry software developed by Radiation Medical Physics at McGill University[13] using planning anteroposterior and lateral chest radiographs (CXRs) with reference to the dummy source(s) placed during bronchoscopy. A remote control afterloading device (Microselection HDR; Nucletron) then inserted a 10-Ci iridium 192 source at the appropriate locations for the determined dwell-times within the hollow catheter. Treatment was delivered in an adjacent, dedicated treatment room monitored by closed-circuit television. Patients were treated with a nominal dose of 800 cGy at a depth of 1 cm from the long axis of the catheter over 10 to 20 min. Patients were treated at 2-week intervals with a goal of three treatment sessions. A follow-up bronchoscopy was then performed 4 weeks following completion of brachytherapy (week 8).

Measured Outcomes

The following outcome variables were evaluated at baseline (week 0) and 4 weeks following the third brachytherapy session (week 8): (1) posteroanterior and lateral CXRs to assess the degree of atelectasis (if present); (2) scoring of signs and symptoms, including hemoptysis, dyspnea, cough, and postobstructive pneumonitis (fever, leukocytosis, and CXR abnormality) using standardized scales ranging from 0 (best) to 4 (worst), developed by Speiser and Spratling;[14] (3) performance status according to the Eastern Cooperative Oncology Group (ECOG) score (0, best, to 4, worst);[15] and (4) still photographs taken at comparable locations from video recordings of the initial and final bronchoscopy. Paired photographs were compared several weeks later by a blinded observer in random order to semiquantitatively assess the degree of endobronchial obstruction. They were rated as improved (>25% decrease in the degree of obstruction), worsened (>25% increase in obstruction), or no change.

Statistical Analysis

Data are expressed as mean±SD. The Welch's t test was used to compare the distribution of baseline characteristics between

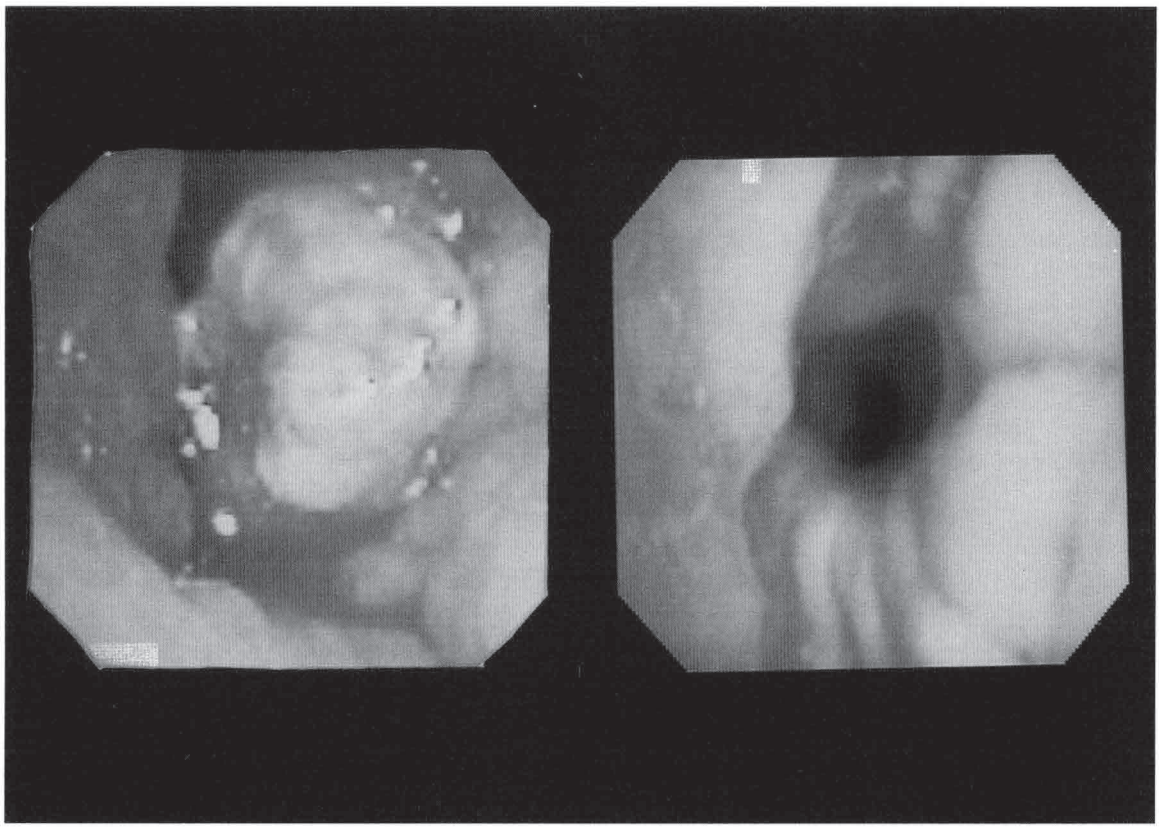

FIGURE 1. Classification of tumor based on endobronchial appearance. *Left,* endoluminal tumor (group 1). *Right,* submucosal infiltration/extrinsic compression (group 2).

groups before treatments.[16] Student's paired *t* test was used for statistical analysis in the comparison of mean symptom scores prebrachytherapy and postbrachytherapy within each of the study groups. Fisher's Exact Test was used to assess the significance of improvements in bronchoscopic appearance and degree of atelectasis on CXR following brachytherapy between the study groups.

RESULTS

Thirty patients were enrolled in the study; 20 had tumor characterized by endoluminal disease (group 1) and 10 by submucosal infiltration and/or extrinsic compression (group 2). Twenty-seven of the 30 patients completed three brachytherapy treatment sessions. Six of the 30 were unavailable for follow-up bronchoscopy at week 8 (four patients in the endoluminal group, two patients in the submucosal group). Three patients unavailable for follow-up had died between weeks 4 and 8 (two in the endoluminal group and one in the submucosal group). These deaths were judged unrelated to a brachytherapy session and were attributed to progressive underlying disease. Baseline characteristics are presented for all 30 recruited patients (Tables 1 and 2). However, the six patients who either died during the study period or were unavailable for follow-up were not included in the statistical analysis.

Bronchoscopic Tumor Appearance as a Determinant of Response

The two study groups (group 1, endoluminal disease, and group 2, submucosal infiltration and/or extrinsic compression) were similar in age and initial ECOG score (Table 1). All patients had completed external irradiation at least 1 month prior to entry in the study (Table 2). The interval between the completion of external irradiation and the commencement of brachytherapy was similar in the two groups, as were the doses of external irradiation and the number of catheters placed per session.

Changes in symptom scores from baseline to 4 weeks postbrachytherapy are shown in Figure 2. Symptoms for the total group tended to improve in all categories; however, only changes in hemoptysis and cough were statistically significant. When the two groups were analyzed separately, there were significant improvements in hemoptysis in both the endoluminal and submucosal/extrinsic compression groups, but only the submucosal/extrinsic compression group had a significant improvement in cough.

Table 1—*Subject Characteristics*

Characteristic	Total	Group 1 (Endoluminal)	Group 2 (Submucosal/Compression)
No. of subjects	30	20	10
Age, yr, mean (range)	64 (36-80)	64 (36-73)	65 (44-80)
Histologic types			
Squamous cell	20	15	5
Adenocarcinoma	7	4	3
Small cell	3	1	2
Stage (TNM)*			
IIIa	12	9	3
IIIb	12	8	4
IV	3	2	1
Small cell			
Limited	1	0	1
Extensive	2	1	1
Initial ECOG score (SD)	1.8 (0.9)	1.8 (0.8)	1.7 (0.9)

*TNM=tumor-node-metastases staging classification.

Improvements in bronchoscopic appearance and CXRs are shown in Table 3. Of those with atelectasis on the baseline CXR, 40% of the patients in group 1 and 50% in group 2 had improvement in the degree of atelectasis over the 8-week study period. Half of the CXRs initially showing atelectasis remained unchanged for both groups. There was no statistical difference in radiographic improvements between the two study groups.

Of the 24 patients who underwent follow-up bronchoscopies, 15 had improvement in the degree of endobronchial obstruction at the end of the 8-week study period. This represented 10 of 16 (62%) in group 1 and 5 of 8 (62%) in group 2. These improvements did not differ significantly between the study groups.

Tumor Location as a Determinant of Response

Ten of 24 patients had tumor predominantly situated in the central airways. Bronchoscopically, 90% of these patients had endoluminal tumor. The other 14 patients had tumor located in more peripheral airways, of whom 7 had tumor characterized bronchoscopically by endoluminal disease and 7 by submucosal infiltration/extrinsic compression.

Changes in symptom scores from baseline to 4 weeks postbrachytherapy are shown in Figure 3. Analysis of symptom scores in the peripheral tumor group showed significant improvements in both hemoptysis and cough. There were no significant improvements in symptom scores in patients with centrally located tumors.

CXRs were also analyzed by tumor location (Table 3). Fifty-four percent of patients with peripheral tumor and atelectasis on the initial CXR showed improvement in the degree of atelectasis, while 38% had no change and 16% worsened. In patients with central tumor, 25% had improvement in the degree of atelectasis on follow-up CXRs. However, there was no statistically significant difference in radiographic improvement between the tumor location groups.

Of the 24 patients who underwent repeat bronchoscopies, 15 had improvement in the degree of

Table 2—*Irradiation Interventions**

Intervention	Total	Group 1 (Endoluminal)	Group 2 (Submucosal/Compression)
No. of subjects	30	20	10
Previous EI, cGy			
Mean dose (SD)	4,298 (1,404)	4,350 (1,380)	4,140 (1,633)
Dose range	2,000-6,900	2,000-6,000	2,400-6,900
Mean no. of fractions (SD)	20 (15)	20 (14)	20 (16)
Interval between EI and brachytherapy, mo			
Mean (SD)	13.8 (21)	13.8 (19)	15.0 (25.2)
Range	1-84	1-72	1-84
Treatment sessions per patient, mean (SD)	2.9 (0.3)	2.9 (0.3)	2.9 (0.2)
Catheters per session, mean (SD)	1.5 (0.5)	1.4 (0.5)	1.6 (0.5)

*EI=external irradiation; p=not significant for all comparisons between group 1 and group 2.

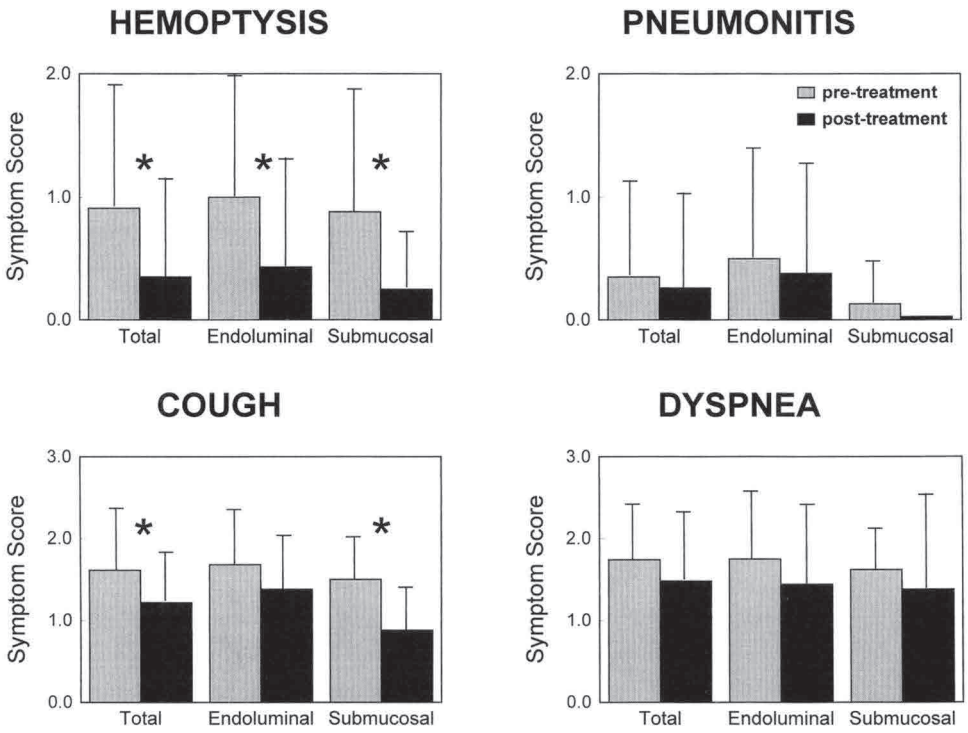

FIGURE 2. Symptom scores prebrachytherapy and postbrachytherapy using numerical indexes ranging from 0 (best) to 4 (worst). Scores are shown for the total group (n=24) as well as for the endoluminal (n=16) and submucosal/extrinsic compression (n=8) groups separately. Hemoptysis was significantly improved postbrachytherapy for the total group as well as both the endoluminal group and the submucosal/extrinsic compression group (asterisk=$p<.05$). However, cough scores improved only in the total and submucosal groups (asterisk=$p<.05$).

endobronchial disease. This represented 50% in the group with central tumor and 71% in the group with peripheral tumor (Table 3). These improvements did not differ significantly between the two groups.

DISCUSSION

The major finding of this study is that patients with endobronchial tumor characterized morphologically by either endoluminal projection or by submucosal infiltration/extrinsic compression can have objective improvements in symptoms following HDR-BT. Furthermore, patients with endobronchial tumor in the more peripheral airways have better symptom response rates compared with patients with central tumors.

Symptoms related to airway involvement are common and problematic in many lung cancer patients. Increasingly, HDR-BT is being used for treatment of local airway tumor, with improvement in symptoms

Table 3—*Summary of the Number of Subjects Showing Improvements in Variables Following Brachytherapy by Subject Group**

		Appearance		Location	
	Total (n=24)	Endoluminal (n=16)	Submucosal (n=8)	Central (n=10)	Peripheral (n=14)
Hemoptysis	11/14†	7/10‡	4/4‡	4/6	7/8‡
Cough	11/24†	6/16	5/8‡	3/10	8/14‡
Dyspnea	8/24	6/16	2/8	3/10	5/14
Pneumonitis	1/5	0/4	1/1	0/2	1/3
CXR (atelectasis)	9/21	6/15	3/6	2/8	7/13‡
Bronchoscopy	15/24	10/16	5/8	5/10	10/14‡

*Denominators reflect the number of subjects with the abnormality at baseline.
†$p<0.01$, posttreatment vs baseline.
‡$p<0.05$, posttreatment vs baseline.

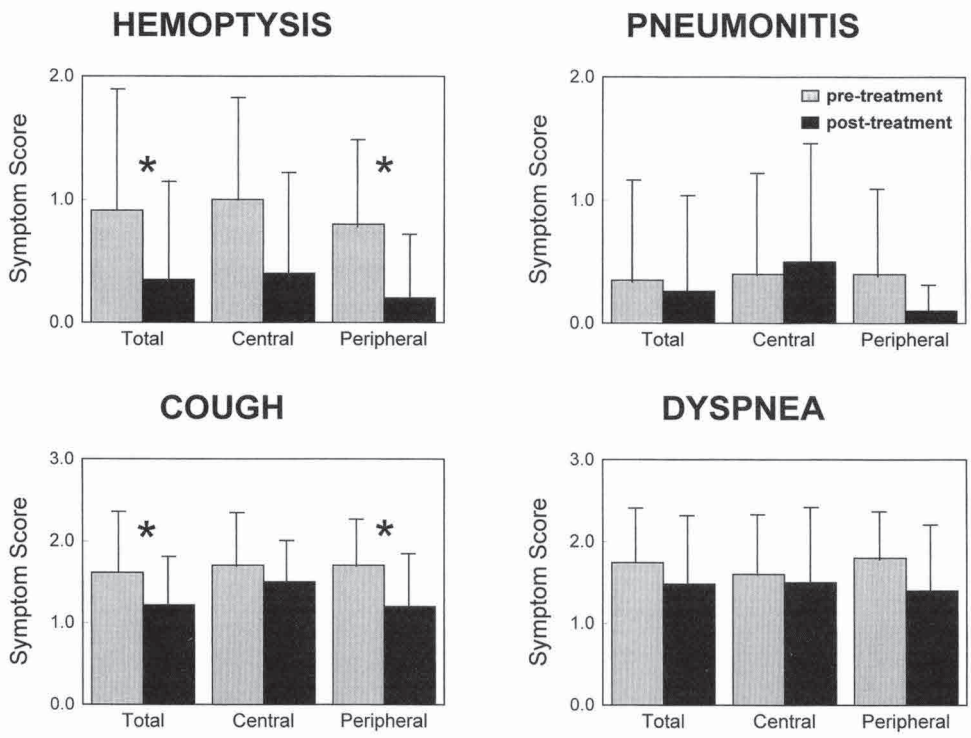

FIGURE 3. Symptom scores prebrachytherapy and postbrachytherapy using numerical indexes ranging from 0 (best) to 4 (worst). Scores are shown for central and peripherally located tumors. Hemoptysis and cough were significantly improved in the total and peripheral tumor groups (asterisk=$p<.05$).

ranging from 50 to 90% in some series.[17] This intervention may be particularly useful in patients who have previously received maximal external irradiation, as in this study, where therapeutic options are limited.[10,11] There are a number of other modalities available to improve airway patency, including laser debulking, airway stenting, and cryotherapy. It has been suggested that tumor characterized by submucosal infiltration and/or extrinsic compression may be best palliated with the placement of airway stents and that endoluminal disease may respond best to a combination of laser debulking and brachytherapy.[18] However, there is little information indicating which factors, if any, might predict a good outcome following HDR-BT.

Bronchoscopic Tumor Appearance

Radiation delivered by HDR-BT is related to the inverse square law, with the intensity of radiation delivered to the tissue falling off inversely as the square of the distance from the radiation source.[19] For example, if the distance from the radiation source is doubled, the intensity of radiation delivered will be a quarter of the original intensity. With this principle in mind, we hypothesized that tumor characterized by submucosal infiltration or extrinsic compression may receive a lower dose of radiation and therefore exhibit less response to HDR-BT than endoluminal tumor adjacent to the treatment catheter.

Our data indicate that patients who present with symptomatic endobronchial disease, regardless of whether disease is endoluminal or submucosal, may show objective improvements in endobronchial obstruction and radiographic abnormalities. Overall response rates in both groups are consistent with those previously reported.[17] Symptom scores tended to improve in most patients; however, the only significant improvements were in hemoptysis (both the endoluminal and submucosal group) and cough (only the submucosal group).

The finding that hemoptysis improved significantly in both the endoluminal and the submucosal infiltration/extrinsic compression groups is not surprising. Although submucosal disease tended to spread extensively along the airway while endoluminal disease was often a discrete projection, the mucosal surface was treated in both cases.

In contrast to hemoptysis, cough scores improved significantly in the submucosal group but not in the endoluminal group. This was not clearly related to improvements in the degree of atelectasis by CXR or endobronchial obstruction since the two groups

demonstrated similar degrees of improvement in both categories. This is not surprising since atelectasis is likely only one mechanism of cough in this group of patients. Other possible mechanisms may be related to secretions and irritation of the tracheobronchial tree or mediastinum, which may have been affected differently by treatment in the two groups.

Tumor Location as a Determinant of Response

We observed that cough and hemoptysis improved significantly only in the group with tumor located at sites distal to the main bronchi. Better response rates in the peripheral airways may be the result of closer proximity of tumor to the radiation source within the airway lumen compared with larger caliber airways. This would result in a higher dose of radiation delivered to the tumor in the former group.[20] Alternatively, the improvement in the group with more peripheral tumor, which bronchoscopically was composed of both endoluminal and submucosal tumor types, may also be a result of less extensive endobronchial disease. Tumor location classification was based on the initial bronchoscopy and the response was based on the degree of patency of the predominant area of disease identified. The patients with centrally located disease had similar response rates with regard to bronchoscopic appearance compared to those with peripheral disease. However, in some cases, as central disease improved, tumor was observed to extend into more peripheral locations that were now rendered visible by bronchoscopy. Therefore, patients with centrally located tumor may have had more extensive endobronchial disease, and the poorer response rates in this group may have been the result of initially unappreciated disease. Central tumor may also be associated with more bulky mediastinal tumor which may account for the poorer response rates. In future studies of this nature, it would be useful to more accurately quantify and localize tumor burden, perhaps with CT imaging.

Study Limitations

Although the number of patients studied was relatively small, this does not detract from the observation that patients with both endoluminal and submucosal tumor may derive significant symptomatic improvements with HDR-BT. While small numbers limited the power to detect more subtle differences, those determined to be significant had the conventional alpha error (false-positive rate) of $<5\%$.

Another potential limitation of this study was the symptom scores used, which tend to be relatively subjective. However, there was unlikely to be a systematic bias as the scores were applied uniformly to all patients.

There was a wide range of time intervals between the completion of external irradiation and the start of brachytherapy, and this variable may have had an effect on the treatment response. For instance, tumor that recurs symptomatically after a brief time interval may behave differently from that which recurs relatively later. However, both endoluminal and submucosal groups had similar mean and median time intervals from the initial treatment, and therefore time is unlikely to have been an important confounding factor.

The Role of Brachytherapy

Patients referred for brachytherapy generally have advanced lung cancer. In this study, subjects had persistent and/or progressive disease despite previous external irradiation. The treatment goals for brachytherapy at our institution are thus palliative rather than curative. With this in mind, the intervention should be acceptable to patients with a minimum of discomfort and without the need for hospitalization. Our results suggest that bronchoscopic tumor appearance does not predict the response to endobronchial irradiation, and hence both subsets of patients can be offered this modality of therapy. With regard to tumor location, peripheral disease appears to have better response rates than more central tumor. Based on these findings, it would be reasonable to consider treating more peripheral tumor with brachytherapy, while combined interventions, such as laser ablation followed by brachytherapy, could be used to attempt to achieve better rates of response in more centrally located tumors. Larger randomized controlled trials would be useful to determine whether combined modality therapy improves symptoms related to airway involvement better than HDR brachytherapy alone, to better define the role of brachytherapy in the palliation of lung cancer.

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References

1 Shields TW. Surgical therapy for carcinoma of the lung. Clin Chest Med 1982; 3:369-87
2 Roach M III, Lediholdt EM Jr, Tatera BS, et al. Endobronchial radiation therapy (EBRT) in the management of lung cancer. Int J Radiat Oncol Biol Phys 1990; 18:1449-54
3 Perez CA, Parjak TF, Rubin P, et al. Long-term observations of patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Cancer 1987; 59:1874-81
4 Tredaniel J, Hennequin C, Zalcman G, et al. Prolonged survival after high-dose rate endobronchial radiation for

malignant airway obstruction. Chest 1994; 105:767-72
5 Sutedja JH, Baris G, Schaake-Koning C, et al. High dose brachytherapy has a curative potential in patients with intraluminal squamous cell lung cancer. Respiration 1994; 61:167-68
6 Suh JH, Dass KK, Pagliaccio L, et al. Endobronchial radiation therapy with or without neodymium yttrium aluminum garnet laser resection for managing malignant airway obstruction. Cancer 1994; 73:2583-88
7 Seagren SL, Harrell JH, Horn RA. High dose rate intraluminal irradiation in recurrent endobronchial carcinoma. Chest 1985; 88:810-14
8 Bedwineck J, Petty A, Bruton C, et al. The use of high dose rate endobronchial brachytherapy to palliate symptomatic recurrence of previously irradiated bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1992; 22:23-30
9 Hernandez P, Gursahaney A, Roman T, et al. High dose rate brachytherapy for the local control of endobronchial carcinoma following external irradiation. Thorax 1996; 51:354-58
10 Glasgow GP, Perez CA. Physics of brachytherapy. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. 2nd ed. Philadelphia: JB Lippincott, 1992; 265-88
11 Hernandez P, Donath D. High-dose-rate endobronchial brachytherapy in the treatment of bronchogenic carcinoma. Chest 1993; 104:989-91
12 Buccheri G, Barberis P, Delfino MS. Diagnostic, morphologic, and histopathologic correlates in bronchogenic carcinoma: a review of 1,045 bronchoscopic evaluations. Chest 1991; 99:809-14
13 Pia C. Fast intracavitary and interstitial treatment planning. In: Mould RF, ed. Brachytherapy 2: proceedings of the Brachytherapy Working Conference. Leersum, Netherlands: Nucletron, 1989; 109-20
14 Speiser BL, Spratling L. Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys 1993; 25:579-87
15 Zubrod CG, Schneiderman M, Frei E. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphate. J Chronic Dis 1960; 11:7-33
16 Glass GV, Hopkins D. Statistical methods in education and psychology. 3rd ed. Boston: Allyn & Bacon, 1996; 295
17 Speiser BL, Spratling L. Intraluminal bronchial irradiation technique: complications and results of protocol treatment in 250 patients. In: Nori D, ed. Proceedings of the International Conference on Thoracic Oncology and Brachytherapy. New York: Nucletron, 1991; 96-98
18 Speiser B, Spratling L. High dose rate remote afterloading brachytherapy in the control of endobronchial carcinoma. In: Mould RF, ed. Selectron brachytherapy journal: pulmonary brachytherapy supplement. Leersum, Netherlands: Nucletron, 1990; 7-15
19 Purdy JA, Glasgow GP, Lightfoot DA. Principles of radiologic physics, dosimetry and treatment planning. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. 2nd ed. Philadelphia: JB Lippincott, 1992; 203
20 Jones B, Bleasdale C, Tan LT, et al. The achievement of isoeffective bronchial mucosal dose during endobronchial brachytherapy. Int J Radiat Oncol Biol Phys 1995; 33:195-99