

Second Line Palliative Endobronchial Radiotherapy with HDR Ir 192 in Recurrent Lung Carcinoma

A. Faruk Zorlu, Ugur Selek, Salih Emri, Murat Gurkaynak, and Fadil H. Akyol

Department of Radiation Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey.

Purpose: To observe the efficiency of reirradiation with high dose rate intraluminal brachytherapy in symptomatic palliation of recurrent endobronchial tumors. **Materials and Methods:** Between January 1994 and June 1998, 21 patients diagnosed with recurrent endobronchial tumors following external beam radiotherapy were treated palliatively with high dose rate intraluminal irradiation at Hacettepe University Oncology Institute. A single fraction of 10 Gy was prescribed to the specified area in 9 patients and 15 Gy to 12. **Results:** Endobronchial treatment improved the performance and reduced symptomatology in 17 (81%) patients. Ten dyspneic patients (10/14, 71%) recovered clinically with an accompanying radiological downstaging. The median symptomatic palliation was 45 days (range, 0 - 9 months), and the overall median survival was 5.5 months (range, 4 - 12 months). The palliative intrabronchial brachytherapy was well tolerated, with the exception of in one patient with a fatal hemorrhage, and another with medically salvaged bronchospasm and intrabronchial edema. **Conclusion:** Recurrent patients with a history of previous thoracic external beam irradiation can be effectively palliated with high dose rate endobronchial reirradiation if the symptoms are directly related to the endobronchial tumor.

Key Words: Endobronchial radiotherapy, brachytherapy, reirradiation, lung cancer

INTRODUCTION

Lung cancer remains a major worldwide health problem and is the leading cause of cancer mortality in both men and women.¹ The majority of those diagnosed have locally advanced stage III (44%) or metastatic stage IV (32%) diseases, and

less than one quarter are potentially operable at diagnosis.¹ Generally, 75% distant metastases and 50 - 75% local recurrence occur in stage III and surgical resection, with consideration for post-operative adjuvant therapy or radiation and chemotherapy, with or without surgical resection, are evaluated to manage the disease. Disease progression within the irradiated field occurs in 33 to 50% of irradiated patients within 15 months.²⁻⁴ A prominent endobronchial disease may worsen the recurrence, with symptoms of cough, obstruction, shortness of breath and severe hemoptysis. The quality of life should be improved in these patients by means of relieving the symptoms, even with a very limited expected survival. Recent advances in techniques, such as laser treatment, brachytherapy, cryotherapy, electrocauterization and intraluminal stents, have equipped the clinician with decent palliation modalities. Endobronchial radiotherapy is a well known option, with minimal complications and rapid fall off of the radiation dose, which spares the normal surrounding tissues,^{5,6} as high dose radiation is delivered to the target. Herein, our experience of palliative endobronchial radiotherapy, on 21 previously irradiated recurrent lung carcinoma patients presenting with endobronchial tumors, is assessed to evaluate efficacy of this modality.

MATERIALS AND METHODS

Twenty-one recurrent non-small cell lung carcinoma (NSCLC) patients were treated with high dose rate (HDR) endobronchial brachytherapy between January 1994 and June 1998. All patients

Received March 2, 2004

Accepted June 5, 2004

Reprint address: requests to Dr. Ugur Selek, Department of Radiation Oncology, Hacettepe University Oncology Institute, Sıhhiye, Ankara 06100, Turkey. Tel: 90-312-3052900, 90-537-7243724, Fax: 90-312-3092914, E-mail: ugurselek@yahoo.com

were admitted to our department with evidence of recurrent endoluminal tumors and persistent symptoms of hemoptysis, cough and dyspnea. All patients had completed external beam thoracic radiotherapy (EBRT) at least 4 months before this study.

All patients had complete systemic and primary work-ups prior to the endobronchial brachytherapy, including a chest X-ray, complete and biochemical blood counts and chest/abdomen computerized tomography. Treatments were applied on an outpatient basis. A respiratory diseases specialist performed a flexible fiberoptic bronchoscopy, under local anesthesia, to visualize the tumor location. A hollow closed ended polyurethane afterloading catheter (5-6F) was then advanced beyond the site of the obstruction. Double catheters were chosen only in 2 patients due to their recurrences in carina. The position of the catheters was verified using direct X-ray films. The application was performed with a high dose rate Ir-192 afterloading system (microSelectron-Oldefit Nucletron, Netherlands). A single fraction dose of 10 Gy was prescribed to the specified area to 1 cm in 9 patients and 15 Gy in 12.

The initial performance was recorded by scoring the Karnofsky Performance Status (KPS). Patients were evaluated with the Speiser Dyspnea Index before and after the treatment (Table 1).⁷

The survival time and symptom control were

calculated from the date of initiation of the endobronchial brachytherapy. Actuarial survival analyses were performed using the Kaplan-Meier method.⁸

RESULTS

Our cohort consisted of 16 males and 5 females, with a median age of 54, ranging from 32 to 70 years. The initial diagnostic staging was stage III A in 16 and stage III B in 5 cases. Pathological diagnosis, by an endoscopic biopsy, revealed a squamous cell carcinoma in 18, an adenocarcinoma in 2 and a bronchoalveolar carcinoma in one. The recurrent diseases, detected from bronchoscopy, were as follows; 12 in the right main bronchus, 6 in the left main bronchus, 2 in the carina and 1 in the lower carina. Previous EBRT had been applied at outside institutions in all but 4 patients, leading to different radiotherapy protocols, with a median total conventional equivalent dose of 30 Gy (range, 30 - 70 Gy) (Table 2). In addition to EBRT, all patients had mainly received cisplatin based chemotherapy protocols before their referral to our institution.

The study group had advanced stage diseases and 5 patients (24%) had distant metastasis at the time of admission to our institute; including 2 in the adrenal glands, 2 in bone and 1 in the brain.

Table 1. Speiser Dyspnea Index

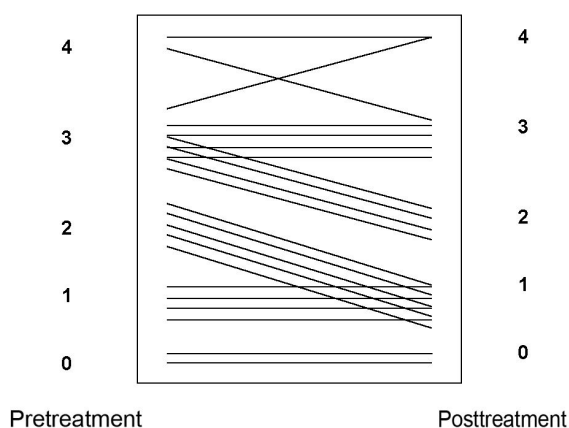
Symptom score	Symptom evaluation
0	No dyspnea
1	Dyspnea on moderate exertion
2	Dyspnea with normal activity, walking on level ground
3	Dyspnea at rest
4	Requires supplement oxygen

Table 2. Initial External Beam Irradiation Schemas of Patients before Recurrence

Patients (n)	Total dose (cGy)	Daily fractions (cGy)
10	3,000	200
5	6,000	200
3	4,480	320
2	3,000	300
1	7,000	200

Table 3. Symptom Relief after Brachytherapy

Complaints	Cases (n)	Cases with relief (%)
Dyspnea	14	10 (71.4)
Hemoptysis	5	4 (80.0)

**Fig. 1.** Dyspnea evaluation with the Speiser Dyspnea Index before and after brachytherapy.

All 21 patients had radiologically or bronchoscopically demonstrated intraluminal tumors, with substantial constitutional symptoms at presentation, with the exception of 2 (2/21, 9.5%) asymptomatic cases. Fourteen (66.7%) patients had severe dyspnea, with evidence of obstruction and atelectasis, which was radiologically visible in 12 (12/14, 85.7%) cases. Five patients (5/21, 24%) had severe hemoptysis that required immediate palliation. The patients demonstrated a broad range of performance status at the time of the protocol initiation, with a mean KPS of 60, ranging from 40 to 90.

The median interval from completion of external irradiation to the onset of brachytherapy was 5.5 months, ranging from 4 to 12 months. Endobronchial treatment improved the performance and reduced symptomatology in 81% of cases (17/21) (Table 3). Ten of the 14 dyspneic patients recovered clinically, with radiological downstaging. Durable symptoms of shortness of breath persisted in 3 of the remaining 4 nonresponsive cases and dyspnea progressed in one patient (Fig. 1). The hemoptysis in 5 patients recovered with the endobronchial brachytherapy, one patient had

sudden fatal hemoptysis on the third postradiotherapy day, which was considered a brachytherapy complication.

The mean period of palliation was 45 days, ranging from 0 to 9 months. The period of palliation was significantly longer in patients with a high KPS (≥ 80) at the initial evaluation ($p = 0.04$). The median survival of all the patients was 5.5 months, ranging from 4 to 12 months. Improved survival was borderline significant in cases with a KPS ≥ 80 ($p = 0.05$).

No serious acute complications developed with the brachytherapy procedure, with the exception of 2 cases; one with fatal hemoptysis and the second with intrabronchial edema that required medical attention.

DISCUSSION

Endobronchial HDR radiotherapy has been easy to apply as an outpatient procedure, with minimum complication rates, and one of the modalities used in the palliation of recurrent intraluminal tumors. Recurrent patients often present with symptoms of cough, obstruction, shortness of breath and severe hemoptysis. Endobronchial radiotherapy may be the first option in eligible recurrent lung carcinoma patients with evident endobronchial tumors. This modality has been observed as a reliable way of palliation in most of our patients.

Recurrent lung carcinoma patients, treated initially with external beam radiotherapy or chemotherapy, are generally not within curable limits. Therefore, palliation becomes the most important end point when survival concerns are absent. On the other hand, assessing the degree of palliation and quantification of symptom relief are not easy. Symptomatic relief was provided to 79% of our patients (15/19), which was reasonably comparable to other published series.^{5,6,9} All

patients with hemoptysis improved with the procedure, and 71% of the dyspneic cases were relieved. However, our median duration of palliation was only 45 days, which was briefly shorter than in other reports, such as the 26 weeks for Gauwitz et al, and the 4.3 months of Seagran et al.^{5,6} It was concluded that this difference in the median duration of palliation was related with the initial patient selection criteria, as the observed duration of palliation was shorter if the KPS was initially low. While patient selection is essential, endobronchial irradiation is known to be more effective and advantageous for survival when primarily considered after definite external beam irradiation.⁷

Brachytherapy is known as an effective palliative method for an advanced disease, either alone or combined with external radiotherapy, and has been shown to be useful with mainly a single fraction of 15 Gy.¹⁰ Fractionated brachytherapy in previously irradiated recurrent patients might be an option to minimize the side effects,¹¹ but one fraction with a single bronchoscopic catheter application seems to provide lower cost and improved patient comfort, without major objective or subjective complications.

Fatal hemoptysis was experienced in only one of our cases, and massive hemorrhages following endobronchial brachytherapy have been reported to range from 25 to 32% in previous studies.^{6,12} No perforation was observed during endoscopy in our subjects, which is not frequent with modern fiberoptic bronchoscopes and flexible catheters. Pneumonia, edema and bronchospasm may be evident after brachytherapy,^{6,12} and intrabronchial edema with bronchospasm was experienced in one of our patients, who was successfully medically managed. No radiation bronchitis and stenosis was detected after the treatments, which are frequently recognized as complications of brachytherapy.^{7,9}

Local treatment modalities, such as laser therapy, cryotherapy and electrocauterization, with or without brachytherapy, are also available to palliate symptoms of endobronchial lesions to obtain tumor regression and relief of obliteration.^{13,14} Implantation of airway prosthetic stents, for airway patency and palliation of bronchogenic carcinoma symptoms, has become another endo-

scopic option when extrinsic airway compression is evident in computed tomography or bronchoscopic evaluation for dyspnea.¹⁵⁻¹⁷ Acute improvement of symptoms and pulmonary function after placement of an endobronchial stent for airway obstruction may be dramatic,^{16,17} but does not help hemoptysis. Transbronchoscopic laser therapy is another easily applicable alternative.¹⁸ Neodymium: yttrium-aluminum-garnet (Nd:YAG) laser is used to resect endobronchial tumors to relieve symptoms. The median survival time after laser resection is about 6 months in primary tumors.¹⁹ However, the requirement of general anesthesia, the increase in bleeding and anatomic deformities and the high prices are leading obstacles. Combination of palliative modalities could be an option to extend palliation duration, but the complication rates might also be increased.

In conclusion, it is our belief that high dose rate endobronchial irradiation can effectively contribute to individual palliation of recurrences in previously irradiated lung carcinoma patients if the presenting symptoms are directly related with the endobronchial tumor lacking any aid to relieve other possible symptoms related with the non-endobronchial component. Accordingly, patient selection seems to be an important parameter to accurately palliate the target patient population; and a longer duration of palliation can only be expected in patients with high performance scores. The combination of brachytherapy with other modalities, such as laser therapy or stent application, needs to be evaluated to possibly offer an effective and longer term palliation.

REFERENCES

1. Jemal A, Thomas A, Murray T, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002;52:23-47.
2. Eisert DR, Cox JD, Komaki R. Irradiation for bronchial carcinoma: reasons for failure. I. Analysis of local control as a function of dose, time, and fractionation. *Cancer* 1976;37:2665-70.
3. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-small-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer* 1980;45:2744-53.

4. Salazar OM, Rubin P, Brown JC, Feldstein ML, Keller BE. Predictors of radiation response in lung cancer. A clinico-pathobiological analysis. *Cancer* 1976;37:2636-50.
5. Gauwitz M, Ellerbroek N, Komaki R, Putnam JB Jr, Ryan MB, DeCaro L, et al. High dose endobronchial irradiation in recurrent bronchogenic carcinoma. *Int J Radiat Oncol Biol Phys* 1992;23:397-400.
6. Seagren SL, Harrell JH, Horn RA. High dose rate intraluminal irradiation in recurrent endobronchial carcinoma. *Chest* 1985;88:810-4.
7. Speiser BL, Spratling L. Remote afterloading brachytherapy for the local control of endobronchial carcinoma. *Int J Radiat Oncol Biol Phys* 1993;25:579-87.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
9. Macha HN, Koch K, Stadler M, Schumacher W, Krumhaar D. New technique for treating occlusive and stenosing tumours of the trachea and main bronchi: endobronchial irradiation by high dose iridium-192 combined with laser canalisation. *Thorax* 1987;42:511-5.
10. Gaspar LE. Brachytherapy in lung cancer. *J Surg Oncol* 1998;67:60-70.
11. Gollins SW, Ryder WD, Burt PA, Barber PV, Stout R. Massive haemoptysis death and other morbidity associated with high dose rate intraluminal radiotherapy for carcinoma of the bronchus. *Radiother Oncol* 1996; 39:105-16.
12. Bedwinek J, Petty A, Bruton C, Sofield J, Lee L. The use of high dose rate endobronchial brachytherapy to palliate symptomatic endobronchial recurrence of previously irradiated bronchogenic carcinoma. *Int J Radiat Oncol Biol Phys* 1992;22:23-30.
13. Nori D, Allison R, Kaplan B, Samala E, Osian A, Karbowitz S. High dose-rate intraluminal irradiation in bronchogenic carcinoma. Technique and results. *Chest* 1993;104:1006-11.
14. Ornadell D, Duchesne G, Wall P, Ng A, Hetzel M. Defining the roles of high dose rate endobronchial brachytherapy and laser resection for recurrent bronchial malignancy. *Lung Cancer* 1997;16:203-13.
15. Sawada S, Tanigawa N, Kobayashi M, Furui S, Ohta Y. Malignant tracheobronchial obstructive lesions: treatment with Gianturco expandable metallic stents. *Radiology* 1993;188:205-8.
16. Bolliger CT, Probst R, Tschopp K, Soler M, Perruchoud AP. Silicone stents in the management of inoperable tracheobronchial stenoses. Indications and limitations. *Chest* 1993;104:1653-9.
17. Vergnon JM, Costes F, Bayon MC, Emonot A. Efficacy of tracheal and bronchial stent placement on respiratory functional tests. *Chest* 1995;107:741-6.
18. Hetzel MR. Current use of lasers in pulmonary disease. *World J Surg* 1983;7:725-31.
19. Brutinel WM, Cortese DA, McDougall JC, Gillio RG, Bergstralh EJ. A two-year experience with the neodymium-YAG laser in endobronchial obstruction. *Chest* 1987;91:159-65.