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Original Articles

High Dose Rate Endobronchial Brachytherapy Effectively Palliates Symptoms Due to Inoperable Lung Cancer

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Background: Intraluminal brachytherapy has become an established treatment for major airway occlusion by relapsed or persistent inoperable endobronchial tumors. The aim of this study was to compare the palliation improvement pre- and post-radiotherapy.

Methods: The study group was 95 patients with the diagnosis of inoperable lung cancer who were eligible for HDR brachytherapy. Fiber-optic bronchoscopy was performed and the level and degree of endobronchial obstruction were estimated in terms of bronchial obstruction index. Endobronchial irradiation was delivered using remote HDR afterloading brachytherapy with iridium-192. Brachytherapy was delivered at weeks 1, 2 and 3 at 7.5 Gy per fraction or at weeks 1 and 2 at 10 Gy per fraction. All patients were evaluated at the beginning and at the third month of therapy. Using Speiser's symptomatic scoring criteria, the severity of symptoms (dyspnea, cough, hemoptysis and postobstructive pneumonia) was weighted. Bronchoscopic findings at the initial evaluation and at the third month were also scored. Surviving patients were followed up for a minimum of 3 months with a mean of 7.5 ± 5.35 months (median: 6 months).

Results: All the symptoms and bronchial obstruction improved significantly after brachytherapy ($P < 0.05$). The most responding symptoms were dyspnea and hemoptysis. The factors determining the complete response were evaluated; age, staging, histological type, lesion localization and previous history of radiotherapy did not seem to determine the complete response ($P > 0.05$).

Conclusions: All the symptoms and bronchial obstruction index seemed to improve after brachytherapy. However, it is difficult to predict the response before the therapy.

Key words: endobronchial brachytherapy – high dose rate – inoperable lung cancer – palliation

INTRODUCTION

The incidence of lung cancer has been increased significantly, ranking as the second among the conditions causing mortality, and also as the leading cause of cancer death (1). Although the search concerning early diagnosis and treatment of several cancer types has shown a great impact on survival, no significant advance has been obtained with lung cancer. Surgical resection affords a chance of cure in only 30% of all cases; however, in only 40% of patients can a fatal outcome be avoided (2). This is even worse in Turkey, where most of the patients are inoperable at the time of diagnosis.

Most patients with endobronchial lesion are not curable and for inoperable patients local treatment of bronchial occlusion may be beneficial, since bronchial occlusion is an important determinant of the quality of life, causing dyspnea, cough, hemoptysis and postobstructive pneumonitis. Treatment options often are limited. Cryosurgery, electrocautery or laser treatment can alleviate only limited bronchogenic carcinoma (3,4). Local tumor control of unresectable lung cancer with

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Abbreviations: EB, endobronchial brachytherapy; ERT, external beam radiotherapy; HDR, high dose rate; LDR, low dose rate; BOI, bronchial obstruction index; PR, partial response; CR, complete response; NR, no response; TR, total response

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Table 1. Speiser's symptomatic scoring index

Hemoptysis	
0	None
1	Less than 2×/week
2	Less than daily but greater than 2×/week
3	Daily, bright red blood or clots
4	Decrease of Hb/Htc >10% greater than 150 cm^3, requiring hospitalization or leading to respiratory distress
Dyspnea	
0	None
1	Dyspnea on moderate exertion
2	Dyspnea with normal activity, walking on level ground
3	Dyspnea at rest
4	Requires supplemental oxygen
Cough	
0	None
1	Intermittent, no medication necessary
2	Intermittent, non-narcotic medication
3	Constant or requiring narcotic medication
4	Constant, requiring narcotic medication but without relief
Pneumonia/elevated temperature	
0	Normal temperature, no infiltrates, WBC <10 000
1	Temperature >38.5 and infiltrate, WBC <10 000
2	Temperature >38.5 and infiltrate and/or WBC >10 000
3	Lobar consolidation on radiograph
4	Pneumonia or elevated temperature requiring hospitalization

Table 2. Speiser's obstruction definitions and scoring criteria

Trachea	>50% = 10, but	<50% = 6, and	<10% = 2
Main bronchus	>50% = 6, but	<50% = 3, and	<10% = 1
Lobar bronchus	>50% = 2, but	<50% = 1	
Atelectasis	2 per lobe		
Pneumonia	2 per lobe		
Total score =			

external beam radiotherapy (ERT) depends on the dose and treatment volume, but has limited normal tissue tolerances. Endobronchial brachytherapy (EB) has been introduced in an attempt to increase the efficiency of the control of malignant airway obstruction and the duration at palliation. Technically low dose rate (LDR) brachytherapy had been used initially; it is now being replaced by high dose rate (HDR) treatment (5).

This paper summarizes our experience with EB and compares palliation rates and complications with others trials.

PATIENTS AND METHODS

Patient Selection

Ninety-five patients who were admitted to the Chest Department and Radiation Oncology Department during May 1997–March 1999 were analyzed in a retrospective study. All of these patients (1) had inoperable lung cancer, proven histologically, (2) had endobronchial tumor, visualized via bronchoscope, (3) were inoperable and (4) were not subjected to standard treatment regimes because of one or more severe symptoms or recurrence after definitive treatment. Speiser's scoring index was used for scoring the degree of endobronchial obstruction (Table 1) (6) and the signs and symptoms of hemoptysis, dyspnea, cough and pneumonitis (Table 2) (5). Performance status was assessed using the ECOG scale. Staging was performed according to the International Staging System for Lung Cancer (7). The characteristics of the patients are shown in Table 3.

Study Groups

Patients were classified according to age, tumor localization (central tumor defined as tumor originating in the trachea or mainstem bronchi; peripheral tumor defined as tumor originating in lobar or segmental bronchi), histological type (defined as squamous cell carcinoma or other types of tumor) and history of prior ERT.

Treatment

After the pretreatment assessment, fiber-optic bronchoscopy was performed transnasally under local anesthesia. The level and the degree of the endobronchial obstruction were estimated in terms of Speiser's bronchial obstruction index. A Lumincath applicator (a 6 cm French flexible nylon catheter) was introduced through the working channel of the bronchoscope into the airway lumen and positioned at least 2 cm beyond to the visible tumor. In 18 cases two catheters were applied because of tumor localization. A radio-opaque 'dummy' wire was inserted for fluoroscopic verification of the catheter position. The patients were then transferred to the Radiotherapy Department where orthogonal radiographs were obtained for dosimetry planning. With these simulation films the treatment plans were made in the three-dimensional planning unit (Nucletron Plato). To perform EB, a catheter was attached to a microselectron HDR remote afterloading unit (Nucletron) that contained an iridium-192 radioactive source. The target volume was described at a depth of 1 cm from the source axis (8). The source was moved in 2.5 mm increments. The total treatment length was 4–8 cm and the total treatment time was 10–16 min. Brachytherapy was delivered at weeks 1, 2 and 3 at 7.5 Gy per fraction or at weeks 1 and 2 at 10 Gy per fraction. In poor performance status patients two fractions were preferred.

The radiobiological equivalent dose (BED) was calculated using the linear quadratic (LQ) radiobiological model for acute-reacting tissues (BED 10), late-reacting tissues (BED 1.7) and tumor (BED 25) (9):

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Table 3. Characteristics of the patients

ECOG score at admission	
1	14 (14.74%)
2	61 (64.21%)
3	17 (17.9%)
4	3 (3.16%)
Histological diagnosis	
Squamous cell cancer	59 (62.1%)
Non-squamous cell cancer	36 (37.9%)
Stage	
IIIB	83 (87.37%)
Primary cases	23 (24.21%)
Recurrent case	60 (63.15%)
IV	12 (12.63%)
Lesion localization	
Central	79 (83.16%)
Peripheral	16 (16.84%)

$$BED = nd[1 + d/(\alpha/\beta)]$$

where n = fraction number and d = fraction dose.

Evaluation

All patients were evaluated at the sixth week and at the third month of therapy. None of the patients received chemotherapy. Four major symptoms were recorded using the Speiser scoring index: dyspnea, cough, hemoptysis and postobstructive pneumonia. The diameters and localization of the tumors, as determined by CT measurements in patients, were correlated with bronchoscopy. Also, bronchoscopic and CT scan findings at the initial evaluation and at the third month were evaluated and scored based on visual assessment by an experienced bronchoscopist.

Statistical Analysis

The Statistical Package for Social Sciences was used to analyze the data. The statistical difference between the symptom scores and bronchoscopic obstruction index before and after brachytherapy was assessed using the Wilcoxon signed rank test. Logistical regression analysis was used to determine the risk factors for symptomatic response. The response in bronchoscopic obstruction index in terms of histological type, lesion location and prior history of radiotherapy was evaluated with the Wilcoxon rank sum t-test. $P < 0.05$ was considered statistically significant.

Table 4. BED value for two or three applications

No. of fraction	Dose of fraction (Gy)	Acute reaction (BED 10)	Late reaction (BED 1.7)	Tumor (BED 25)
2 (EB)	10	40	137.6	28
3 (EB)	7.5	39.75	121.7	29.75
23 (ERT)	2	55.2	100.1	49.68

RESULTS

Follow-up

Surviving patients were followed up for a minimum of 3 months with a mean of 7.5 ± 5.35 months; 59 patients were followed up for more than 6 months. The prognosis of patients who were out of follow-up was recorded by calling their homes and obtaining information from their relatives by May 2000.

Of the 95 patients enrolled in the study, 7 were female. The mean age was 60 ± 7 (range: 41–81 years); 60 patients have received external beam radiotherapy previously (large field, A–P, 46 Gy) and 35 patients had no history of prior external beam radiotherapy. BED values are shown in Table 4.

The median value of the symptom scores and bronchial obstruction index at admission and at the third month are shown in Fig. 1. In Table 5 the risk parameters that affect the response rate of patients to radiotherapy were compared at the main symptoms in inoperable lung cancer. All the symptoms and bronchial obstruction index improved significantly (Table 6) ($P < 0.001$). The best improvement was in the bronchial obstruction index and dyspnea. The role of lesion location in improvement is shown in Figs 2–6. The symptom scores and bronchial obstruction index seemed to be improved significantly in patients with a central lesion. In the peripheral lesion group pneumonia did not show a significant improvement after the therapy, but the improvement in other scores and bronchial obstruction index was significant ($P < 0.01$). An interesting observation was that in patients who had never received prior ERT, cough response rates were higher, although this was not statistically significant. No statistically significant difference was observed when the patients were classified according to histological type or evidence of prior ERT.

Short-term Outcome

Transient non-cardiogenic chest pain occurred in nine patients. None of the patients died as a complication of the therapy. On the fifth week one patient (1%) had hemoptysis requiring hospitalization and it was relieved after symptomatic therapy. One patient (1%) died in the eighth week of the therapy due to cranial metastasis. None of the patients experienced pneumothorax, fistula or cardiovascular problems. At follow-up bronchoscopies, especially with a history of ERT, dry mucosa with varying degrees of stenosis sometimes associated with a mucous plug was observed. These were not clinically significant.

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Table 5. Evaluation of the risk parameters determining complete response

	Hemoptysis	Dyspnea	Cough	Pneumonia
Age	–0.0420	0.0224	–0.0028	0.0754
	0.0508	0.0322	0.0393	0.0435
	0.9589	1.0227	0.9972	1.0783
	(0.4079)	(0.4871)	(0.9434)	(0.0833)
Stage (stage IV)	0.2586	0.5855	–0.1257	0.9228
	0.5829	0.3500	0.6323	0.5743
	1.2951	1.7958	0.8819	0.1081
	(0.6573)	(0.0943)	(0.8425)	(0.1081)
Histological type (other than squamous cell carcinoma)	–0.2630	0.1755	–0.5157	
	0.3194	0.2512	0.3146	
	0.7687	1.1919	0.5971	
	(0.4102)	(0.4846)	(0.1011)	
Lesion localization (peripheral tumor)	–0.0435	–0.0575	0.4868	0.7791
	0.3882	0.3768	0.4197	0.5842
	0.9574	0.9441	1.6271	2.1794
	(0.9108)	(0.8787)	(0.2462)	(0.1823)
Previous history of ERT (prior ERT)	0.0962	–0.0833	0.1682	
	0.3330	0.2488	0.3300	
	1.1010	0.9200	1.1832	
	(0.7727)	(0.7376)	(0.6102)	

*Values are logistical regression coefficients, standard errors and relative risks with *P* values shown in parentheses.

One patient died 4 months after treatment, five patients after 6 months, two patients after 12 months and one patient after 14 months. No information could be obtained about the prognosis of 33 patients. One patient died due to cranial metastasis (see above). From the information obtained from the relatives, none of the patients died as a consequence of massive hemoptysis.

DISCUSSION

Airway obstruction and related symptoms worsen the quality of life in lung cancers. The most important consideration in these patients is to restore the patency of the airway. Different therapeutic modalities are available for palliation. These are external beam radiation, endobronchial radiotherapy, laser therapy, phototherapy, stent application and different combinations of these techniques (10,11). Endobronchial brachytherapy is one of these effective modalities (12).

Our results support the efficacy of HDR brachytherapy as a palliative therapy modality. In our study, brachytherapy showed a significant improvement in terms of symptom scores and bronchial obstruction index. The improvement in bronchial obstruction index supports the fact that endoscopic clearing is correlated with improvement of the symptoms. In our study we tried to evaluate the determinants of response. Dyspnea, hemoptysis, cough and bronchial obstruction showed significant improvements in both central and peripheral tumor groups, with the improvement in dyspnea and hemoptysis being more significant in the central tumor group. No significant improvement was obtained in pneumonia in the peripheral tumor group whereas the central tumor group showed a statistically significant improvement. These results are in contrast with the study reported by Ofiara et al., in which only cough and hemoptysis improved in the total and peripheral tumor group (8). Inclusion of patients with submucosal infiltration and/or extrinsic compression could have an impact on these contradictory results.

In our study, no significant difference was obtained in palliation rates between the patients who had received prior radiotherapy and those with no history of external radiotherapy. This may confirm the results in which the addition of external radiation to brachytherapy had no impact on the clearing of endobronchial disease.

Table 6. Comparison of pre- and post-treatment symptomatic scores

Symptom	*Z*–value	*P*
Dyspnea	–7.36	<0.05
Cough	–5.63	<0.05
Hemoptysis	–5.89	<0.05
Pneumonia	–4.74	<0.05
BOI	–8.26	<0.05

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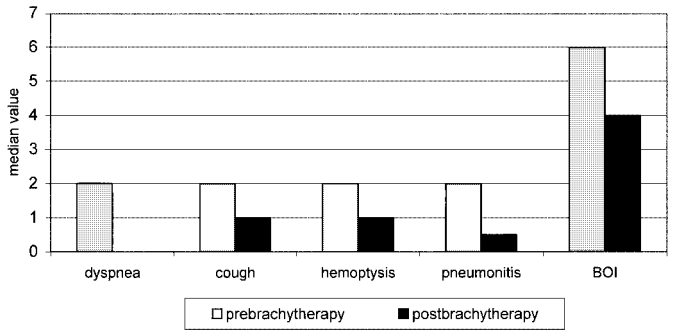


Figure 1. Symptoms and palliation rates before and after brachytherapy.

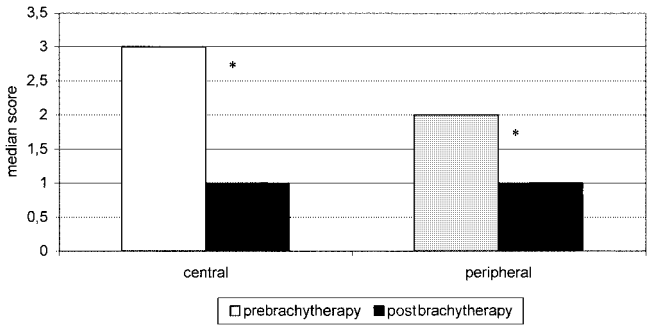


Figure 4. Improvement of hemoptysis pre- and post-treatment when the patients were grouped according to lesion location. *$P < 0.05$.

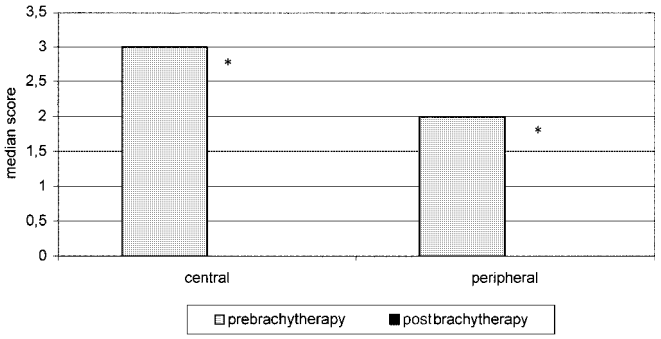


Figure 2. Improvement of dyspnea pre- and post-treatment when the patients were grouped according to lesion location. *$P < 0.05$.

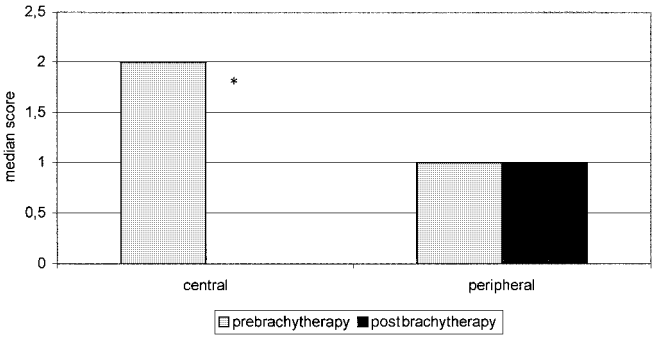


Figure 5. Improvement of pneumonitis pre- and post-treatment when the patients were grouped according to lesion location. *$P < 0.05$.

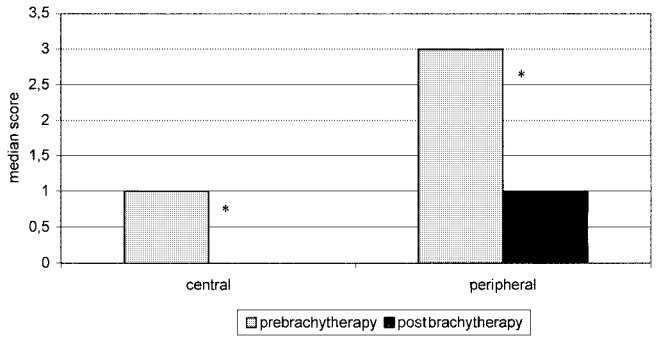


Figure 3. Improvement of cough pre- and post-treatment when the patients were grouped according to lesion location. *$P < 0.05$.

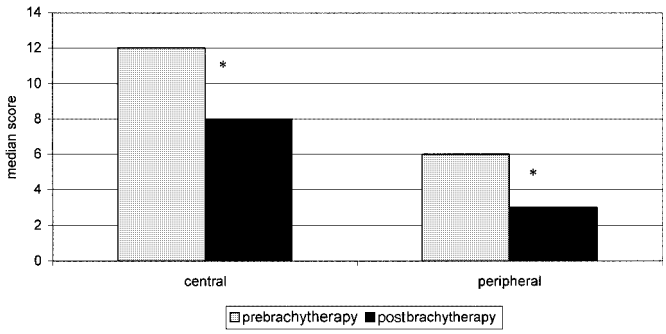


Figure 6. Improvement of bronchial obstruction index (BOI) pre- and post-treatment when the patients were grouped according to lesion location. *$P < 0.05$.

We made another classification according to histological type but no significant difference in terms of response rates was observed ($P > 0.05$).

Another analysis was performed to evaluate the determinants of complete response but gender, age, staging, histological type, lesion localization and history of previous external beam radiotherapy seemed to have no impact on complete response (13).

The complication rate was very low. Only one patient had massive hemoptysis requiring hospitalization, and no brachytherapy-related complication other than this occurred. No local side effects except transient pleuritic pain were observed in our patients. Speiser and Spratling reported that the complication rate increased with concurrent radiotherapy, curative patient, prior photoresection and large cell type (14). Cotter et al. reported that the mean total dose for patients with no complication was 79.05 Gy and the mean implant dose was 15.21 Gy (15). On long-term follow-up, no massive bleeding which is a long-term complication of brachytherapy occurred (16). The highest fatal hemorrhage was reported by Khanavkar et al. (17). In Speiser and Spratling's study they found that the most effective dose and fractionation scheme was 7.5 Gy at a 10 mm depth in three fractions once a week (5). Additionally we applied brachytherapy in two fractions to patients who had

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poor performance status. This may explain the very low complication rate and also, although we did not intend to evaluate dose and fractionation rates in this study, the high symptom palliation rates due to treatment and the low complication rates may indicate that the dose schedule is safe and effective.

In conclusion, HDR brachytherapy is a successful palliative therapy modality at 7.5 Gy at a 10 mm depth in three fractions once per week or 10 Gy twice. However, it is difficult to predict the response in patients before the therapy.

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