Survival Benefits of Lung Cancer Patients Undergoing Laser and Brachytherapy

We aimed to compare the duration of survival among subjects receiving brachytherapy (BT) in combination with Nd:YAG laser therapy (LT), and those receiving LT or BT alone. The medical records of subjects who received endobronchial treatment for unresectable tracheobronchial malignancies between January 1997 and December 1999 in a single center were reviewed retrospectively. A total of 80 patients were evaluated. The overall symptomatic response rate after treatment was 86.5%. Median survival durations for the LT, BT, and combined therapy (CT) group were 111, 115, and 264 days, respectively. The survival duration was significantly longer in the CT group than in the BT group (p=0.0078), but the difference was not statistically significant between the CT and the LT group. The bronchoscopic finding of endobronchial polypoid lesion was associated with a longer survival time than extraluminal with compression type (p=0.0023) by univariate analysis. Other factors associated with the better prognosis included hemoglobin ≥12.5 g/dL, serum albumin level ≥37 g/L, and BT dose ≥15 Gy at 1 cm distance. Of these factors, specific bronchoscopic findings, serum albumin level, CT modality, and dose of BT retained statistical significance in multivariate analysis. In conclusion, combined LT and BT is associated with increased patient survival compared with BT alone. Combined therapy may improve survival time in selected patients with endobronchial malignancies.

Key Words : *Lasers; Brachytherapy; Mixed Tumor, Malignant; Survival*

Tae Won Jang, Glen Blackman*,
Jeremy J George[†]

Department of Internal medicine, Kosin University
College of Medicine, Busan, Korea; Department of
Radiotherapy*, Thoracic Medicine[†], University
College London Hospitals. London, U.K.

Address for correspondence
Tae Won Jang, M.D.
Department of Internal Medicine, Kosin University
College of Medicine, 34 Amnam-dong, Suh-gu,
Busan 602-702, Korea
Tel : +82.51-990-6637, Fax : +82.51-248-5686
E-mail : jangtw@ns.kosinmed.or.kr

INTRODUCTION

The majority of patients diagnosed with lung cancer have advanced disease, and only 15-20% are candidate for surgery at the time of diagnosis (1). Metastases to the lung are common, and endobronchial metastatic tumor deposits mimicking a primary bronchogenic carcinoma are well documented (2). Local progression of lung malignancy that affects the airway, either endobronchially or by extrinsic compression, occurs in almost 80% of patients, and many become symptomatic with dyspnea or post-obstructive pneumonia. As a result, many patients with inoperable lung malignancy require palliative treatment (3). Bronchoscopic treatment of airway malignancies is usually considered in patients with surgically unresectable lesions, and is aimed at relieving obstructive symptoms rather than curing the neoplasm.

The standard method of palliating symptoms of patients with inoperable non-small cell carcinoma is external beam radiotherapy (EBRT), which has limitation of slowness in response and morbidity proportional to radiation dose. There is therefore a need for alternative treatment modalities. The endobronchial therapies including the techniques of laser

therapy (LT), brachytherapy (BT), prosthetic stents, cryotherapy, photodynamic therapy, radiofrequency, and electrocautery have brought important improvements in the control of lung tumors. LT for malignant tumors is purely palliative and should be performed in unresectable case (4). The laser provides immediate and often dramatic relief of symptom in patients with localized obstruction of the large airways caused by endobronchial tumor. However, it is not effective in managing patients with extrinsically compressed airways and the duration of symptomatic relief may be very brief (5). BT is used to deliver radiation therapy from within the airway lumen to treat malignant tumors that obstruct the airways. In general, high dose rate brachytherapy (HDR-BT) is a good palliative treatment, and well tolerated with few reported complications (6, 7).

The use of HDR-BT as a component of therapy for locally advanced non-small cell lung cancer (NSCLC) has been described, but its benefits has not been proven; no significant benefit in survival has yet been achieved, except in selected groups (8, 9), and the survival benefit has not been compared to that of external beam radiotherapy alone (10, 11). The combination of endobronchial LT with other palliative therapies

is possible and can extend the duration of palliation. The combined therapy (CT) with LT and BT may lead to an increased survival in patients, compared to those undergoing a single treatment modality. However, there are few published data showing the survival benefits of the CT (12). This study was undertaken to examine the length of the survival of patients who had undergone CT compared with LT or BT alone in a single center utilizing high-dose [192]Iridium (Ir) in the treatment of malignant lung cancers through a retrospective analysis.

MATERIALS AND METHODS

The medical records of patients who had undergone LT or BT from January 1997 to December 1999 at the Middlesex Hospital, University College London Hospitals were reviewed. We recorded patients' characteristics, prognostic factors including stage, pathologic cell type, bronchoscopic findings, treatment modality, technical details of the BT, symptomatic response, survival time, and complications. Data on death were obtained from, mainly, data of Thames Cancer Registry, notification of death forms in medical records, and reply letters from General Practitioners.

The patients were divided into three groups according to whether they had been treated with LT, BT, and CT. Survival was measured from the date of the first episode of LT or BT. We classified bronchoscopic findings using a classification system modified by Bucheri et al. (13). Endobronchial nodular and infiltrative type (EN) was defined as an endobronchial mass presenting as either a predominantly intraluminal nodular growing mass or mucosal infiltration. Endobronchial polypoid (EP) type was defined as an intraluminal lobulated fleshy growth. Extraluminal with compression (EC) referred to a tumor with an irregular area of mucosal surface with infiltration, or any form of deformation, or narrowing of bronchi.

The details of LT and BT techniques have been reported elsewhere (4, 14). All LT was undertaken under general anesthesia. Both rigid and flexible bronchoscopes were used in most cases. LT was given first to debulk tumors of the trachea or main bronchi. BT in most cases was given one week after LT in the CT group. The catheter was advanced using a nasal approach if possible, under direct vision, and placed either beyond or adjacent to the obstructing mass. The bronchoscope was then removed over the catheter and a dummy source with radio-opaque marking at 1 cm intervals was inserted through the treatment catheter. The treatment was carried out using an HDR remote afterloading system (Micro-Selectron; Nucletron Oldelft Corp; Veenendaal, Netherlands) with a high activity source. Both the chest physician and radiotherapist determined the target volume, which included 1 to 2 cm security margins on both sides of the main obstructed airway segment considering its location and length. After each treatment session (lasting 5 to 10 min), the catheter was removed. A sec-

ond procedure was performed when required on a clinical basis. The response to BT was assessed in 4 to 6 weeks.

Statistical Analysis

Data were analyzed using the Excel and SPSS statistical software packages for Windows and expressed as percentages or means±standard deviation (SD). Statistical significance was evaluated by Student t-test, paired t-test, bivariate correlation, and multiple analysis of variances (one-way ANOVA). For univariate analysis, survival rates were calculated using the Kaplan-Meier method. The p values were based on the log-rank test (15). A simultaneous assessment of the effects of different prognostic factors was performed within a multiple regression analysis using the Cox model (16). Statistical significance was set at $p < 0.05$.

RESULTS

Ninety-four patients were enrolled. Of these patients, data from 14 were not included in the analysis (stent treatment in 6, insufficient information in 6, and benign tumor in 2). Eighty patients were included in this study, consisting of 56 men and 24 women. Sixty-seven had a primary lung cancer and 13 had a metastatic lung cancer. The predominant histological type in the biopsies obtained was squamous cell cancer (54%), followed by adenocarcinoma (14%), and 4 cases of small cell lung cancer were included (5%). Patients' characteristics are shown in Table 1. Twenty-two subjects were treated with LT, 37 with BT, and 21 with CT. Groups were comparable with respects to age, white blood cell count, hemoglobin, platelet count, calcium, alkaline phosphatase, alanine aspartate, bronchoscopic findings, and stage, but the serum albumin level of the CT group was significantly higher than those in the other two groups (p=0.028, one-way ANOVA). Seventy-five patients (94%) had tumors of advanced stage or recurrent tumor. Five patients with operable stage in whom surgery was contraindicated due to poor lung function were included. Prevalence of squamous cell carcinoma significantly increased with age (Pearson's correlation coefficient, 0.371; p=0.001). Up to 82.9% of the patients had undergone prior treatment for cancer; 52.6% had received a single modality of treatment, and 30.3% had received two or more. The most common previous treatment modality was EBRT (85.7%). The primary cancer of metastatic lung cancer included renal cell carcinoma (3 cases), esophageal cancer (2 cases), and one each case of adrenocortical tumor, cholangiocarcinoma, colon cancer, endometrial carcinoma, laryngeal tumor, malignant fibrous histiocytoma, malignant melanoma, and ovarian cancer. Seventy-four patients (92%) had died, and six patients were lost to follow-up (8%) at the time of the retrospective study.

The mean dose of BT was 12.5 Gy at 1 cm from the source.

Table 1. Patient characteristics by treatment modality

	Total	LT group	BT group	CT group
No. of patients	80	22	37	21
Age (yr)	64.7±12	65.6±12.8	65.3±11.4	62.4±12.6
Gender (male/female)	56/24	14/8	30/7	16/5
Diagnosis				
Primary lung cancer	67	17	34	16
Metastatic lung cancer	13	5	3	5
Pathology				
Squamous cell ca.	42	11	18	13
Adeno/Large cell ca.	14	4	6	4
NSCLC non-specified	9	4	5	0
Small cell ca.	4	0	3	1
Others	9	3	3	3
Location				
Tracheal invasion	17	6	6	5
Major bronchi	49	15	20	14
Lobar bronchus	11	1	9	1
Bronchoscopic finding*				
EN type	39	12	19	8
EP type	24	10	3	7
EC typ	18	0	12	6
Stage				
I-IIIa	5	3	0	2
IIIb	35	6	20	9
IV	20	10	6	4
Recurrent tumor	18	3	9	6
Laboratory finding[†]				
Hb	12.5±1.9	12.2±1.2	12.4±2.0	12.9±2.2
Albumin (g/L)[‡]	36.4±5.3	34.8±1.4	35.8±4.5	39±4.4
Calcium (mmol/L)	2.41±0.14	2.39±0.15	2.43±0.16	2.40±0.12

*p=0.028 among groups (one-way ANOVA).
[†]All values are expressed as mean±SD.
[‡]p=0.079 among groups (one-way ANOVA).
ca, carcinoma; LT, laser therapy; BT, brachytherapy; CT, combined treatment; EN, endobronchial nodular and infiltrative; EP, endobronchial polypoid; EC, extraluminal with compression.

Table 2. Results of technical factors in brachytherapy (n=54)

	Mean	Minimum	Maximum
Active source (cGy/m²/hr)	3,366.2	1,650	9,325
Total dose (Gy)	12.5	5	22.5
Time (sec)	364.5	145	848
Number of catheter	1.05	1	2
Active length (cm)	5.08	4	8
Frequency	1.11	1	3

Table 3. Symptomatic response after treatment

	Total (%)	LT	BT	CT
Yes	45 (86.5)	15 (83.3)	13 (81.3)	17 (94.4)
No	7 (13.5)	3 (16.7)	3 (18.8)	1 (5.6)

*Assessment of response in brachytherapy group was done 4-6 weeks after treatment.
LT, laser therapy; BT, brachytherapy; CT, combined treatment.

Table 4. Univariate survival estimates for patients from time of first therapeutic bronchoscopy

	No.	MST (days)	95% CIs (days)	p value
Stage				
I-IIIa	5	494	245-743	0.0061*, 0.0017[†]
IIIb-IV	55	115	78-152	
Recurrent disease	18	174	105-242	
Treatment modality				
LT group	22	111	24-198	
BT group	37	115	77-153	
CT group	21	264	168-359	0.1411[‡], 0.0078[§]
Bronchoscopic finding				
EN type	39	138	94-182	
EP type	20	215	42-380	0.0757[∥], 0.0023[¶]
EC type	18	115	48-182	
Brachytherapy dose				
≥15 Gy at 1 cm	27	199	130-268	0.0077
< 15 Gy at 1 cm	27	98	57-139	
Hemoglobin				
≥12.5 g/dL	42	211	131-291	0.001
< 12.5 g/dL	37	98	75-121	
Serum albumin level				
≥37 g/L	40	205	77-337	0.0046
< 37 g/L	34	66	0-133	
Symptomatic response				
Yes	47	181	95-226	0.0147
No	7	104	1.4-206	
Pathology				
Squamous cell carcinoma	42	138	101-175	0.1041
Other pathologic types	36	98	75-120	
Diagnosis				
Primary lung cancer	67	126	96-155	
Metastatic lung cancer	13	269	126-412	0.135

*Stage I-IIIa vs IIIb-IV (log-rank test).
[†]Stage I-IIIa vs recurrent disease (log-rank test).
[‡]LT vs CT (log-rank test).
[§]BT vs CT (log-rank test).
[∥]EN type vs EP type (log-rank test).
[¶]EP type vs EC type (log-rank test).
MST, median survival time; CI, confidence interval; LT, laser therapy; BT, brachytherapy; CT, combined treatment; EN, endobronchial nodular and infiltrative; EP, endobronchial polypoid; EC, extraluminal with compression

Fifty-three patients (91%) received a single session of BT, four patients did two sessions, and only one patient did 3 sessions. The mean dose received by the BT group was 12.3±3.8 Gy, and that by the CT group was 12.7±4.5 Gy (p=0.719). Table 2 lists the technical details of the BT. The mean length of tissue treated, 5.08 cm, was accounted for by the 1 to 2 cm margins of security on both side of the tumor site. Up to 86.5% of patients experienced relief from their symptoms, subjectively. The symptomatic response rate of the CT group was higher than those of the other groups, but the difference was statistically not significant (Table 3).

The estimated overall median survival time was 138 days (95% CI, 100-175 days) with actuarial 1-yr survival rate of
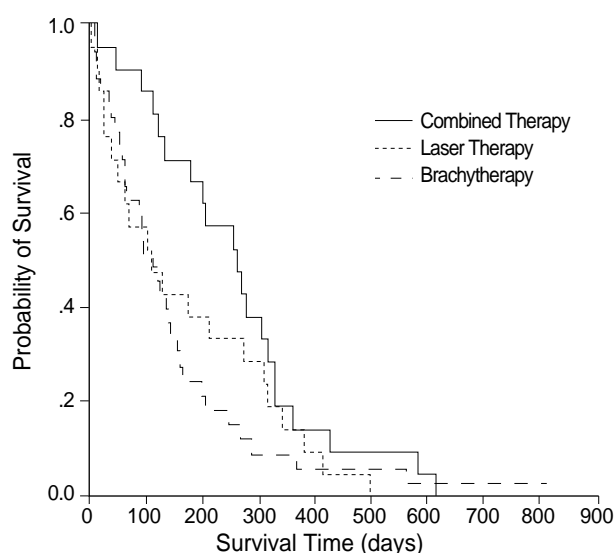
Fig. 1. Survival estimates by treatment modality in all patients with malignant tumors.
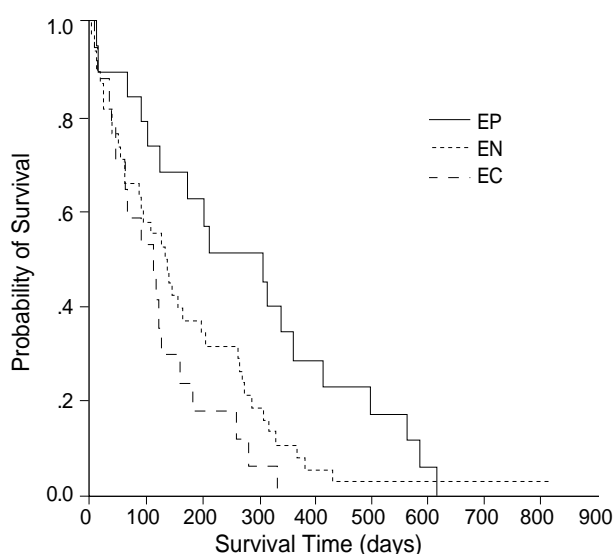

Fig. 2. Survival estimates according to bronchoscopic finding. EP, endobronchial polypoid type; EN, endobronchial nodular type; EC, extraluminal compression type.

Fig. 3. Survival estimates by radiation dose of brachytherapy.

Table 5. Cox multivariate regression model

Variable	Coefficient	SE	HR (95% CI)	p value
Albumin	-0.072	0.04	0.931 (0.870-0.966)	0.039
Brachytherapy dose	-0.113	0.04	0.888 (0.818-0.965)	0.005
CT	-0.764	0.39	0.466 (0.217-0.999)	0.05
Bronchoscopic finding				0.02
EP vs EN	-0.77	0.52	0.463 (0.166-1.289)	0.14
EP vs EC	-1.009	0.37	0.365 (0.178-0.746)	0.006
EC vs EN	0.238	0.51	1.269 (0.471-4.418)	0.037

EN, endobronchial nodular and infiltrative; EP, endobronchial polypoid; EC, extraluminal with compression

12.3%. Table 4 gives the detailed results of univariate analysis. The median survival time was 264 days in the CT group, while the LT and BT groups had lower median survival times of 111 days and 115 days, respectively (p= 0.1411 for CT vs LT and p=0.0078 for CT vs BT). The median survival in the CT group is 2.3 times longer than those in the other groups, but there was no statistical significance between LT and CT group. The survival profile of the Kaplan-Meier estimate by treatment modality is shown in Fig. 1. Analyses of survival on the bronchoscopic findings revealed that the median survival time for the EP type was longer than those for the EN and EC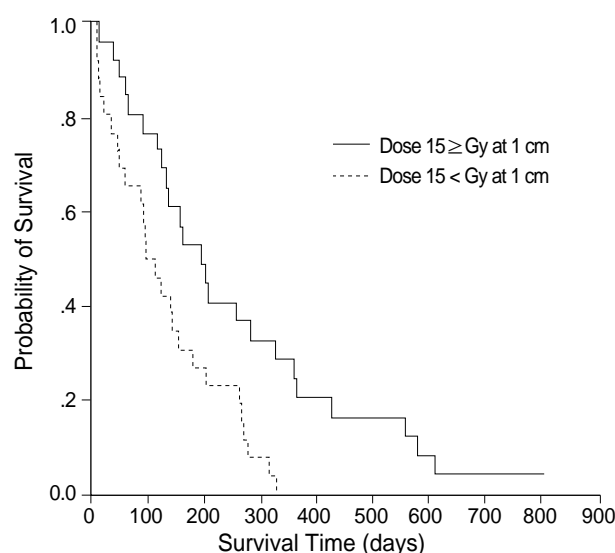 types, but a statistical significance was only between EP and EC type (p=0.0023; survival curves shown in Fig. 2). The following factors were associated with a better prognosis: hemoglobin $\geq$12.5 g/dL (p=0.001), dose of BT $\geq$15 Gy at 1 cm (p=0.0041, Fig. 3), serum albumin level $\geq$37 g/L (p=0.0046), and presence of a symptomatic response (p=0.0147). White blood cell count, platelet count, alkaline phosphatase, and aspartate transaminase were not associated with survival outcome. Likewise, squamous cell carcinoma histology, primary vs metastatic lung cancer, gender, presence of tracheal involvement, age $\geq$65 yr-old, and previous EBRT were not implicated in the survival. According to the results of this univariate analysis, hemoglobin, albumin, dose of BT, bronchoscopic findings, and treatment modality were the covariates selected for potential inclusion in a multivariate Cox regression model. The model selected included albumin (p=0.0039), dose of BT (p=0.005), CT modality (p=0.05), and bronchoscopic findings (p=0.02). The full model is presented in Table 5.

There was no procedure-related death. The complication rates were similar with 8 cases in 53 sessions (15.1%) in LT, and 9 cases in 62 sessions (14.8%) of BT. Fever occurred in 1 case after LT and in 4 cases after BT. Four cases of minor

Table 6. Complications after procedures

	LT (n=53)	BT (n=62)
Fever	1	4
Hemoptysis (< 100 mL)	3	1
Pneumothorax	1	0
Respiratory failure	2	4
Cardiac arrhythmia	1	0
Total (% of complication)	8 (15.1%)	9 (14.6%)

LT, Nd-YAG laser therapy; BT, brachytherapy.

hemoptysis (less than 100 mL) was encountered in 5 cases, however, none required specific treatment or admission to hospital. Respiratory failure occurred in 2 cases after LT and 4 cases after BT, and responded well to supportive care (Table 6).

DISCUSSION

EBRT often provides excellent local control and is the mainstay of palliative therapy for bronchogenic cancer, however local recurrence and extension is common (17, 18). These patients may be candidates for LT and BT. There have been few reports on the survival benefits of BT alone. Long-term survival was observed rarely in selected cases whose tumor size was limited (8, 9). There are several potential advantages of BT used as an adjuvant to the LT in treating malignant airway disease. It is well known that radiotherapy and chemotherapy are poorly effective in the treatment of the endobronchial component of tumors (19, 20). Laser techniques should be limited to endobronchial exophytic tumor tissue to a limit of 3-4 mm from the bronchial mucosa. BT reaches tumor components in the bronchial mucosa and in the wall up to a depth of 5-6 mm, depending on the dose given. BT is thus complementary to laser techniques. Some studies have suggested that patients who had undergone CT experienced an improvement in their quality of life, less disease progression, and a reduction in the cost of treatment (14, 21). Only a few studies have compared the survival benefit of CT with that of single treatment modalities. Shea et al. (12), also in a retrospective study, reported that the addition of BT might increase the duration of patient survival compared to the palliation with LT alone. The survival benefit they demonstrated was limited to subjects with squamous cell carcinoma, and the results of our series do not support this finding. Their analysis did not include the BT alone group. Miller and Phillips (22) suggested that CT improved local control of tumor compared with either modality alone; however, due to the limited follow-up in the CT group, possible correlation with survival could not be revealed.

Bronchoscopic finding is an important factor in predicting treatment response. Taulelle et al. (23) reported that the size of the extrinsic component of a tumor was related to treatment results. They found a complete response rate of 62% in cases with a limited extrinsic component as compared to 44% when the extrinsic component was greater than 50% measured by computed tomography. However, there has been no general agreement on this point, since the presence of a predominant extrinsic component is not considered to be a relative contraindication to the method by other authors, especially if EBRT is used in association with BT (11, 22). Our study showed a longer survival time in subjects with endobronchial tumors, especially of the polypoid type. This is likely to be because LT and BT are mostly effective in reducing intraluminal mass, but are less effective on extraluminal components. The indications for BT in patients with extraluminal compression type lung cancer must be carefully considered from our results. Ofira et al. (24) indicated that patients presenting with symptomatic endobronchial disease, regardless of whether the disease was endobronchial or submucosal, showed objective improvement in endobronchial obstruction and radiographic abnormalities following BT, but they could not demonstrate survival differences. The prognostic implication of laboratory parameters has not been as studied extensively in NSCLC. Low serum albumin level has been shown to have poor prognostic implication in some studies, as well as low hemoglobin level (25, 26). Our results also suggest that pretreatment normal hemoglobin and albumin levels are associated with a better prognosis, however, since the size of our study population is small, this observation needs further verification.

Numerous reports have shown that BT is a very effective technique, but no standardized fraction schedule has been currently established. Langendijk et al. (27) reported that the risk of massive pulmonary hemorrhage increased dramatically when a fraction size of 15 Gy was used. However, Gollins et al. (9) indicated that there was no overall difference in the actuarial survival curves by 20 Gy compared with 15 Gy, therefore a dose of 17.5 Gy at 1 cm from the central axis of the source might represent an ideal compromise for single fraction treatment. In one study using a single shot technique, 20 Gy BT at 1cm distance from the source was associated with a significantly higher rate of fatal hemorrhage than lower doses (6). Our results revealed that the higher dose BT was associated with significant survival benefit, but we had to consider the complication rate. In palliative care, a low complication rate has an important effect on the quality of life. Accurate calculation of the cumulative dose of irradiation is of great importance to minimize side effects. Our study showed that a dose of 15 Gy higher at 1 cm distance from the source was associated with longer survival time without major complications. A dose of 15 Gy at 1 cm may be appropriate in the palliative setting

The major complications directly attributable to the procedures such as fistulae, lung abscesses, massive hemorrhage, and perforation were not seen in our study. Our fraction doses were relatively low, which is one factor related to the absence of major complications. In one study (28), five of 18 patients

died of massive hemorrhage. It is unclear if this was related to disease progression or was a direct result of therapy. Hennequin et al. (29) reported that hemoptysis is usually due to disease progression, whereas radiation bronchitis is significantly influenced by tumor location and technical factors such as dose and volume. We may have incompletely ascertained cases of massive hemorrhage and other late complications due to the retrospective nature of our analysis, and incomplete medical records held at the tertiary referral center. Patients with locally advanced disease in whom the primary cause of death is failure of other organ systems may not have lived long enough to develop complications. Fatal hemorrhage peaked at a mean of 10.5 months after the first treatment, suggesting there may be a late reaction due to radiation overdose, which needs to be taken into account (29). Some authors reported the high risk of complications associated to the CT (10, 30), but Cella et al. (14) reported there were neither morbidity nor mortality related to the treatment. This is comparable with our results.

The limitation of our study is its retrospective nature. In this setting, information such as performance status, the degree of airway obstruction, radiological evaluation of the malignant neoplasm, symptom index, details of follow-up bronchoscopy, and late complications of treatment might not be routinely reported, obtained, or not be available for evaluation, and therefore not be included. Another limitation is the heterogeneity of the study subjects. There were many kinds of histological type, different previous treatment histories, uneven distribution of stage and bronchoscopic finding, and a wide variation in patients' characteristics. Furthermore, there was a wide range of time intervals between the completions of external irradiation or chemotherapy and the start of therapeutic bronchoscopic treatment, and this variable may effect on the survival time. The observation that prior treatment factors, histological type, sex, and tumor location did not have a significant effect on patient's prognosis in our analysis suggests that these factors are unlikely to be important confounding factors.

We think the reasons for prolonged survival in the CT group to be as follows. The first is a mechanical effect; as the size of the mass is reduced after LT, the penetration of BT into the residual tumor will be increased. Secondly, LT may have promoted the tissue oxygenation and radiation damage by the increased blood flow as a result of the local inflammation relating laser irradiation and biologic effects such as increasing blood flow within a tumor. Thirdly, differences in baseline characteristics between the groups may have affected the survival outcome. Uneven distribution of the endobronchial type of tumor that is known to be more amenable to treatment by LT/BT may be a relevant factor.

Our study suggests that patients treated with BT in combination with LT survive for longer time than those treated with BT alone. However, a prospective randomized study with longer follow-up is needed to determine the true extent of this survival benefit. The continuing evolution in BT may contribute to improvement of existing results. Our data suggest that CT not only relieve symptoms, but also prolong survival in selected patients. We believe that the combination of laser resection with endobronchial radiotherapy is an effective technique for patients with endobronchial obstructing tumors at an advanced stage, and a technique useful not only for palliation of symptoms but also possibly associated with survival benefit.

ACKNOWLEDGMENT

REFERENCES

1. Fry WA, Menck HR, Winchester DP. *The national cancer data base report on lung cancer. Cancer 1996; 77: 1947-55.*

2. Braman SS, Whitcomb ME. *Endobronchial metastasis. Arch Intern Med 1975; 135: 543-47.*

3. Carrol M, Morgan SA, Yarnold JR, Hill JM, Wright NM. *Prospective evaluation of a watch policy in patients with inoperable non-small cell cancer. Eur J Cancer Clinic Oncol 1986; 22: 1352-6.*

4. Cavaliere S, Foccoli P, Toninelli C. *Endobronchial laser treatment. European Respiratory Monograph 1998; 9: 49-64.*

5. George J. *Endoscopic laser resection for tracheobronchial malignancy. Thorax 1996; 13: 437-41.*

6. Macha HN. *Endobronchial high dose rate brachytherapy. European Respiratory Monograph 1998; 9: 65-78.*

7. Nori D, Allison R, Kaplan B, Samara E, Osian A, Karbowitz S. *High dose rate intraluminal irradiation in bronchogenic carcinoma: technique and results. Chest 1993; 104: 1006-11.*

8. Tredaniel J, Hennequin C, Zalcman G, Walter S, Homasson JP, Maylin C, Hirsh A. *Prolonged survival after high-dose rate endobronchial radiation for malignant airway obstruction. Chest 1994; 105: 767-72.*

9. Gollins SW, Burt PA, Barber PV, Stout R. *Long term survival and symptom palliation in small primary bronchial carcinoma following treatment with intraluminal radiotherapy alone. Clin Oncol 1996; 8: 239-46.*

10. Aygun C, Weiner S, Scariato A, Spearman D, Stark L. *Treatment of non-small cell lung cancer with external beam radiotherapy and high dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1992; 23: 127-32.*

11. Speiser BL, Spratling L. *Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys 1993; 25: 579-87.*

12. Shea JM, Allen RP, Tharratt RS, Chan AL, Siefkin AD. *Survival of patients undergoing Nd:YAG laser therapy compared with Nd:YAG laser therapy and brachytherapy for malignant airway disease. Chest 1993; 103: 1028-31.*

13. Buccheri G, Barberis P, Delfino M. *Diagnostic, morphologic, and histopathologic correlates in bronchogenic carcinoma. A review of 1,045 bronchoscopic examinations. Chest 1991; 99: 809-14.*

14. Cella A, Ambrogi MC, Ribechini A, Mussi A, Fabrini MG, Silvano G, Cionini L, Angeletti CA. *Combined Nd-YAG laser/HDR brachytherapy versus Nd-YAG laser only in malignant central airway involvement: a prospective randomized study. Lung Cancer 2000; 27: 169-75.*

15. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Petp J, Smith PG. *Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1976; 34: 585-612.*

16. Cox DR. *Regression models and life tables (with discussion). J R Stat Soc B 1972; 34: 187-220.*

17. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, Brown GS, Concannon J, Rotman M, Seydel HG. *A prospective randomized study of various irradiation and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung. Cancer 1980; 45: 2744-53.*

18. Rabie T, Wilson RK, Easley JD, Teague RB, Bloom K, Lawrence EC, Ilaria R. *Palliation of bronchogenic carcinoma with [198]Au implantation using the fiberoptic bronchoscope. Preliminary report by the radiation therapy oncology group. Chest 1986; 90: 941-5.*

19. Chetty KG, Moran EM, Sassoon CS, Viravathana T, Light RW. *Effect of radiation therapy on bronchial obstruction due to bronchogenic carcinoma. Chest 1989; 95: 582-84.*

20. Hazuka MB, Bunn PA Jr. *Controversies in the nonsurgical treatment of stage III non-small cell cancer. Am Rev Respir Dis 1992; 145: 967-77.*

21. Allen MD, Baldwin JC, Fish VC, Goffinet DR, Cannon WB, Mark JBD. *Combined laser therapy and endobronchial radiotherapy for unresectable lung carcinoma with bronchial obstruction. Am J Surg 1985; 150: 71-7.*

22. Miller JI, Phillips TW. *Neodynium: YAG laser and brachytherapy in the management of inoperable bronchogenic carcinoma. Ann Thorac Surg 1990; 50: 190-6.*

23. Taulelle M, Chauvet B, Vincent P, Felix-Faure C, Buciarelli B, Garcia R, Brewer Y, Reboul F. *High dose rate endobronchial brachytherapy: results and complications in 189 patients. Eur Respir J 1998; 11: 162 -8.*

24. Ofiara L, Roman T, Schwartzman K, Levy RD. *Local determinants of response to endobronchial high-dose rate brachytherapy in bronchogenic carcinoma. Chest 1997; 112: 946-53.*

25. O'Connel JP, Kris MG, Gralla RJ, Groshen S, Trust A, Fiore JJ, Kelsen DP, Heelan RT, Golbey RB. *Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small cell lung cancer treated with combination chemotherapy. J Clin Oncol 1986; 4: 14-22.*

26. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. *Survival determinants in extensive stage non-small cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991; 9: 1618-26.*

27. Langendijk JA, Tjwa MK, de Jong JMA, ten Velde GPM, Wouters EFM. *Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: is*

28. Seagren SL, Harrell JH, Horn RA. *High dose intraluminal irradiation in recurrent endobronchial carcinoma. Chest 1985; 88: 810-4.*

29. Hennequin C, Tredaniel J, Chevret S, Durdux C, Dray M, Manoux D, Perret M, Bonnaus G, Homasson JP, Chotin G, Hirsh A, Maylin C. *Predictive factors for late toxicity after endobronchial brachytherapy: a multivariate analysis. Int J Radiat Oncol Biol Phys 1998; 42: 21-7.*

30. Khnavker BL, Stern B, Alberti W, Narkosteen JA. *Complications associated with brachytherapy alone or with laser in the lung cancer. Chest 1991; 99: 1062-5.*