External Beam Radiation Therapy combined with Airway Stenting leads to Better Survival in Patients with Malignant Airway Obstruction

Christopher Mallow, MD¹, Jeffrey Thiboutot¹, Roy Semaan, MD², Margaret M. Hayes, MD³, Russell Hales, MD⁴, Ashwin Ram, MD⁴, David Feller-Kopman, MD¹, Hans Lee, MD¹, and Lonny Yarmus, DO¹

¹Section of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

²Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

³Harvard Medical School, Beth Israel Deaconess Medical Center, Division of Pulmonary and Critical Care Medicine, Boston, MA

⁴Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Background and objective—Malignant airway obstruction, a common complication of patients with advanced lung cancer, causes debilitating dyspnea, and poor quality of life. Two common interventions used in the treatment of malignant airway obstruction include bronchoscopy with airway stenting and external beam radiotherapy. Data are limited regarding their clinical effectiveness and overall effect on survival.

Methods—A retrospective chart review of patients, treated with airway stenting and/or external beam radiotherapy at the Johns Hopkins Hospital for malignant airway obstruction between July 2010 and January 2017 were reviewed. Demographics, performance status, cancer histology, therapeutic intervention and date of death were recorded. Survival was calculated using cox regression analysis.

Results—Out of 606 patients who were treated for malignant airway obstruction, 237 were identified as having malignant airway obstruction and included in the study. 68 patients underwent rigid bronchoscopy and stenting, 102 external beam radiotherapy and 67 a combined approach. Patients who underwent stenting had an increased hazard ratio of death in comparison to those who received combination therapy (HR 2.12, 95% CI 1.02,4.39), while there was a trend towards significance in the EBRT alone group in comparison to the combination therapy group (HR 1.62, 95% CI 0.93,2.83).

Conclusion—In this retrospective analysis, combination therapy with stenting and EBRT led to better survival in comparison to stenting or EBRT alone. Prospective cohort trials are needed to confirm these results.

Keywords

Lung cancer; bronchoscopy and interventional techniques; clinical respiratory medicine

INTRODUCTION

Malignant airway obstruction (MAO) occurs in approximately 30% of all patients with advanced stage lung cancer¹ and can lead to debilitating dyspnea, cough and hemoptysis. These symptoms significantly impair quality of life². Once MAO is diagnosed, the average survival can be as low as 1–2 months if left untreated³.

The three main treatment modalities used for the symptomatic relief of MAO are external beam radiotherapy (EBRT), rigid bronchoscopy with tumor excision/destruction, dilation and airway stent placement and combination therapy using both of these interventions. These modalities have not been compared and there is currently no gold standard. Little data exist on their efficacy and effectiveness. In a retrospective analysis of 50 patients, airway stenting was shown to increase survival in patients with intermediate performance status in comparison to poor performance, with an overall median survival of 117 days⁴. Another retrospective review of 65 patients showed an average median survival of 6.2 months post-stenting⁵. In a retrospective review of 43 patients who received both stenting and EBRT, the overall survival was shown to be 3.44 months⁶. There was a significant difference in the survival of stented patients who received full course therapy in comparison to patients who had to have EBRT stopped early (8.4 months vs 21 days, respectively)⁶. Additionally, the direct impact of these treatments on survival is poorly understood⁷, and there has not been a comparison of treatment modalities at a single center. This retrospective study focuses on a single centers clinical experience with MAO treatment using rigid bronchoscopy with airway stenting and radiotherapy.

METHODS

This was a retrospective chart review study conducted at The Johns Hopkins Hospital from July 2010 through January 2017. Approval was obtained from the Johns Hopkins University institutional review board (IRB#: NA_00081563) prior to initiation of data collection. Current Procedural Terminology (CPT) codes: 31631 (tracheal stent), 31636 (bronchial stent) 31637 (additional bronchial stent) and 77401–77416 (external beam radiotherapy) were used to identify patients who had undergone palliative bronchoscopy with airway stenting or EBRT for malignant airway obstruction during the pre-defined dates. Charts were reviewed to exclude patients who had an intervention for non-malignant disease. All patients with malignant airway obstruction were reviewed by a multidisciplinary tumor board, represented by medical oncology, radiation oncology, interventional pulmonology and thoracic surgery. Patients subsequently underwent the procedure that by the board was felt to be most beneficial for the patient.

Demographic information, including age, gender, race and income was collected via chart review. Additional information such as smoking history (current/former smoker versus non-smoker), chemotherapy regimen, level of obstruction, degree of obstruction and Eastern Cooperative Oncology Group (ECOG) performance status score at the time of diagnosis were also collected if available. The level of obstruction and degree of obstruction were estimated via bronchoscopy or CT scan measurements. The patient's cancer stage and histology including sub-type for non-small cell lung cancer was noted. Type of therapeutic intervention and date and the order they received the interventions in the EBRT/stent combination group was recorded, with dual treatment within 30 days considered treatment at the same time. Dates of death were recorded from the chart and verified using the social security death index (SSDI) and via medical records.

Statistical analysis

Baseline characteristics were compared among the three treatment modalities using multiple methods. For continuous variables, linear regression was used to determine whether there was a difference between interventions. For dichotomous variables, logistic regression was applied. With categorical variables, multinomial logistic regression was conducted to detect a difference. To determine a difference in means between the three intervention groups, analysis of variance was conducted. When a statistically significant difference was found, simple t test or tests of proportions were used to investigate differences between two groups at a time. Missing data was assumed to be at random.

For survival analysis, median survival by treatment type based on the time of intervention to the date of death or a pre-determined administrative censor date of July 1, 2017 were calculated using the method of Kaplan-Meier. The log-rank test was used to detect differences in the probability of survival between the three treatment arms. Univariate cox proportional hazard analysis was conducted to determine risk factors associated with increased or decreased mortality. Multivariate cox proportional hazard was performed using variables that were associated with increased or decreased mortality on univariate analysis, or determined to be clinically meaningful. Proportional hazard assumption testing was performed by examination of schoenfeld residuals. All statistical analyses were performed using STATA IC, version 14.2 (College Station, TX).

RESULTS

A total of 606 patients with malignant airway obstruction were identified. Those with non-malignant airway obstruction (NMAO) were excluded. The remaining 237 (39%) had malignant airway obstruction and were included in the final analysis (Figure 1). 68 (28.7%) were treated with rigid bronchoscopy with tumor excision/destruction and stenting, 102 (43%) were treated with EBRT alone, and 67 (28.3%) patients received both therapies. The baseline characteristics of the patients in the three treatment arms are shown in Table 1. Among patients that received both interventions, 72% received them at the same time and there was no significant difference between those who received stenting or EBRT first ($p=0.644$).

Among the three intervention groups, the median time of death in the stent only, EBRT only and combination groups was 113.5 days, 84.5 days and 157 days, respectively. The overall mortality between the three groups was not significantly different. Patients in the stent group had a mortality rate of 63.2%, the EBRT group was 65.7% and the combined group had a mortality of 68.6%.

The Kaplan-Meier curve is shown in Figure 2. When conducting cox proportional hazard modeling, there was no violation of proportional hazards. Interactions were tested between smoking and malignancy, and intervention and ECOG, with no significant interaction identified. After adjusting for age, race, ECOG score, chemotherapy, degree of obstruction and type of malignancy, the use of stenting had an increased hazard of death in comparison to combination therapy (HR=2.12, 95%CI 1.02,4.39) (Table 2). There was a trend toward increased hazard of death for the EBRT only group in comparison to the combination therapy group (HR=1.62, 95%CI 0.93, 2.893). There was no association with increased hazard of death by malignancy type, smoking status, age, race or female sex. ECOG scores of 2 and 3 were also associated with a statistically significant increased hazard of death. There was no association between hazard ratio and degree of obstruction, or location of obstruction. There was an increased hazard ratio of death for those who received combination therapy at the same time, in comparison to those who received therapies further apart in a univariate cox model analysis (HR= 3.39, 95%CI 1.68, 6.87) which continued to be significant in the adjusted model (HR=4.46, 95%CI 1.05,18.98). There was no association with level of obstruction (in comparison to tracheal obstruction), or with severity of obstruction and hazard of death (p=0.24 and p=0.69, respectively).

DISCUSSION

Malignant airway obstruction is a common complication in patients with advanced stage lung cancer as well as those with metastatic non-lung primaries, that leads to decreased quality of life and ultimately to death, usually within 1–2 months if left untreated³. Although three major interventions, bronchoscopy with airway stenting, EBRT, and combination stenting with EBRT, are used to treat malignant airway obstruction, there is a paucity of comparative survival data between them. Currently, no prospective, randomized data exist, and thus our retrospective analysis adds significantly to the field. Although survival in all arms of the study was poor, we found that combination therapy of EBRT with stenting was associated with better survival as compared to EBRT or stenting alone. There was also no difference between EBRT and stenting as single therapy.

We believe that the most meaningful clinical risk factors addressed in this study included location of obstruction, degree of obstruction, ECOG score and presence of concomitant chemotherapy. Interestingly, after adjustment, there did not appear to be a survival difference for any of the above other than ECOG. This is reassuring, as elevated ECOG scores have been well known to be associated with worse survival⁸. There was also an association between receiving chemotherapy and decreased hazard of death, another expected finding to further substantiate our findings.

We postulate that the reason patients undergoing rigid bronchoscopy with airway stenting in combination with EBRT had better survival due to the immediate relief of the mechanical obstruction provided by bronchoscopy and the lasting effects of radiation. Immediate, i.e. within minutes, relief compared to days to weeks needed for EBRT to take effect, may prevent other downstream effects of continued obstruction, such as hemoptysis, atelectasis, and post obstructive pneumonia. Palliative EBRT is generally given as 3 Gy per fraction up to a total of 30 Gy therapy⁹ and takes up to two weeks to deliver the total dose. Clearly, the goal of EBRT is not only to treat the endobronchial obstruction, but to definitively treat the *cause* of the obstruction. EBRT and endobronchial stenting have their unique side effect profiles, with pneumonitis being associated with EBRT and migration, granulation tissue formation associated with airway stent placement. EBRT may also treat more distal airways where bronchoscopic therapies and airway stenting may not be feasible.

Though our results are intriguing, there are several limitations that suggest a large, multi-center trial should be conducted. The retrospective single center nature of the study, limited us to the data available in the chart. Additionally, patient selection and referral bias were not able to be fully controlled for however, at our center, all patients are reviewed by a multidisciplinary tumor board represented by medical oncology, radiation oncology, interventional pulmonology and thoracic surgery. In this discussion, all potential therapeutic options are openly discussed and a consensus agreement results in procedural selection chosen based on what is perceived as the safest and most effective procedure for these patients at that time. As EBRT does not require sedation or anesthesia with its associated risks, sicker patients with MAO and higher American Society of Anesthesia (ASA) scores may have been sent for EBRT. This self-selection of sicker patients for EBRT may provide an alternative explanation for the difference in median time to death in this group compared to the stenting and combination groups. However, the results were still significant when adjusting for the proportion of patients in the study where ECOG score was recorded (58% of the patients). All treatment modalities were done in a tertiary care center, which limits the generalizability of the study. And perhaps the most important limiting factor is the lack of randomization. Given the retrospective nature of this study, it was not possible for us to randomize patients to one of the three arms.

Our study examined patients that underwent both modalities for MAO with a significant survival advantage found as compared to stenting or EBRT alone. Although the majority of patients received both treatments at the same time, those who received stenting first did not differ in survival in comparison to those who received EBRT first. Interestingly, those that received both therapies within 30 days of one another did have a trend toward worse outcomes. Given the circumstances, these patients likely had more severe disease than the cohorts that received one therapy at a time. Survival in patients with MAO, where bronchoscopy has failed to re-cannulate the airway, has been shown to be worse in a prospective study¹⁰, possibly introducing another element of bias. Another limitation is that we were only able to focus on survival not on health related quality of life¹¹. Given that the lives of these patients are limited, being symptom free is of the utmost importance, but the retrospective study design prevented this analysis, however this is an important factor to investigate in prospective studies.

In conclusion, malignant airway obstruction can cause significant distress, anxiety, dyspnea, cough and pain. Three major treatment modalities, bronchoscopy with airway stenting, EBRT and combination stenting with EBRT, were examined in a retrospective fashion by which combination therapy demonstrated better survival outcomes. We believe that the use of combination airway stenting and EBRT therapy is warranted in this patient population, as it shows a survival benefit. Prospective randomized trials would be beneficial to further investigate this, but unfortunately it would be difficult to perform without excluding patients that present with severe dyspnea, given their need for immediate bronchoscopic intervention. It is possible, however, that a randomized trial could be designed for all other patients that present with findings of malignant airway obstruction.

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SUMMARY AT A GLANCE

Malignant airway obstruction is a complication for lung cancer patients. Multiple modalities exist for the treatment of this ailment, including airway stenting and external beam radiotherapy. We showed retrospectively that airway stenting combined with external beam radiotherapy was associated with increased survival in comparison to either treatment in isolation.

Figure 1. Patient Flow Chart

A total of 606 patients who were identified with CAO, 237 of which were due to malignancy (MAO) and 369 were due to other causes (NMAO). Of the 240 patients, 68 received an airway stent only, 102 received EBRT only and 67 received both treatments.

Figure 2. Kaplan-Meier Curve by Intervention Type

Kaplan Meier Curve illustrating survival in days, separated by treatment modality.

Table 1

Baseline characteristics

	Stent (n=68)	EBRT (n=102)	Both (n=67)	P Value
Demographics				
Gender - %				0.48
Female	47.1	38.2	38.8	
Race - %				0.55
White, not Hispanic	63.2	63.7	64.1	
Black, not Hispanic	32.4	21.6	29.9	
Other	0.4	14.7	6	
Age - yrs				<0.01 [*]
Mean	58.4	65.6	59.2	
Tobacco Use- %	70.2	87.3	79.1	0.02 ^{**}
Performance Status- Mean				0.004 [±]
±ECOG	1.4	1.97	1.51	
Type of Malignancy- %				<0.02 [^]
SCLC	7.4	22.5	11.9	
NSCLC	52.9	66.7	58.2	
Other	39.7	10.8	29.9	
Location of Obstruction- %				0.02 ^a
Trachea	32.4	5.8	25.4	
Right Main Stem	20.6	8.8	31.3	
Left Main Stem	19.1	5.8	17.9	
Right Bronchus Intermedius	19.1	9.8	14.9	
Right Upper Lobe	1.5	20.6	1.5	
Right Middle Lobe	0	13.7	0	
Right Lower Lobe	0	7.8	3.0	
Left Upper Lobe	4.4	14.7	0	
Lingula	0	4.9	0	
Left Lower Lobe	2.9	7.8	6.0	
Degree of Obstruction- %				<0.01 ^{^^}
Complete	38.2	30.7	50	
Severe (75–99%)	52.9	37.6	40.9	
Moderate (50–75%)	7.4	29.7	9.1	
Mild (<50%)	1.5	2	0	

^{*} EBRT vs Stent and EBRT vs Both (p<0.001).

^{**} Stent vs EBRT (p=0.007).

[±] Stent vs EBRT (p=0.007).

[^] SCLC- Stent vs EBRT (p=0.006). "Other" cancers- Stent vs EBRT (p<0.001) and EBRT vs Both (p=0.002).

^aTrachea- EBRT vs Stent ($p<0.001$) and EBRT vs Both group ($p<0.001$). Right Main Stem- EBRT vs Stent ($p=0.02$) and EBRT vs Both ($p<0.001$). Left Main Stem- Stent vs EBRT group ($p=0.01$). Right Upper Lobe- EBRT vs Stent ($p<0.01$) and EBRT vs Both ($p<0.01$). Right Middle Lobe- EBRT vs Stent ($p<0.01$) and EBRT vs Both ($p<0.01$). Right Lower Lobe- EBRT vs Stent ($p=0.02$) and EBRT vs Both ($p=0.02$). Left Upper Lobe- EBRT vs Stent ($p=0.03$) and EBRT vs Both ($p<0.01$).

^{^^} EBRT vs Both for complete obstruction ($p=0.012$). Stent vs EBRT for severe obstruction ($p=0.049$). Stent vs EBRT and EBRT vs Both for moderate obstruction ($p=0.0005$ and $p=0.0008$, respectively).

Table 2

Hazard ratios for death, for covariates unadjusted and adjusted for type of malignancy, age, race, ECOG score, chemotherapy and degree of obstruction.

	Unadjusted Hazard Ratio	Unadjusted 95% CI	* Adjusted Hazard Ratio	Adjusted 95% CI
[±] Intervention				
Stent	1.25	0.82,1.91	2.12	1.02,4.39
EBRT	1.54	1.05,2.26	1.62	0.93,2.83
Age	1.01	0.998,1.03	1.01	0.99,1.04
Tobacco Use	1.17	0.79,1.72	0.59	0.32,1.13
Race	1.11	0.88,1.41	0.96	0.68,1.36
Female Sex	1.00	0.73,1.38	1.24	0.77,1.99
[¥] ECOG				
1	1.73	0.53,5.66	1.93	0.56,6.72
2	3.06	0.92,10.12	3.78	1.06,13.50
3	7.05	2.07,24.06	7.59	2.03,28.32
4	4.91	0.80,30.12	5.48	0.74,40.56
^{**} Cancer Subtype				
NSCLC	0.90	0.58,1.38	0.68	0.39,1.20
Other	0.73	0.45,1.2	0.55	0.24,1.24
^{±±} Degree Obstruction				
Severe	0.95	0.67,1.35	0.89	0.55,1.46
Moderate	0.81	0.51,1.29	0.74	0.41,1.35
Mild	1.60	0.39,6.57	3.44	0.41,28.76
Receiving Chemotherapy	0.63	0.45,0.89	0.98	0.58,1.66

* Adjusted for type of malignancy, age, race, ECOG score, chemotherapy and degree of obstruction.

[±] Comparative group is the stent and EBRT combined cohort.

[¥] Comparative group is an ECOG score of 0.

^{**} Comparative group is the SCLC subtype.

^{±±} Comparative group is complete obstruction.