Lung Cancer Related Central Airway Obstruction: Who Benefits Better from Radiotherapy?

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ABSTRACT

We aimed to assess the efficacy of external beam radiotherapy (EBRT) in central airway obstruction (CAO) and associated factors for metastatic lung cancer (MLC) patients. Records of 72 MLC patients presenting with CAO were retrospectively analyzed. The serial chests X-rays prior and after the EBRT were compared for response assessment. The primary end-point was radiologic response, while overall- (OS) and CAO-free survival, and predictors of better outcomes constituted secondary endpoints. The EBRT doses ranged between 8 to 40 Gy (1-13 fractions). Median follow-up and OS were 5.6 (range: 1.3-17.8) and 7.6 months (95% CI: 6.5-8.7), respectively. Objective CAO resolution was achieved in 58 patients (80.6%) on serial chest X-rays with a median time to maximum CAO response of 23 days (range: 3-86). In responders the response was durable (8.1 months) almost nearly for all their remaining life spans (8.3 months) with only 19.0% CAO recurrences. Median OS was also significantly longer in responders (8.3 vs. 2.4 months; p< 0.001). Small-cell histology (p= 0.002), tumor size <5.3 cm (p= 0.007), and biologically equivalent dose (BED10) ≥39 Gy (p< 0.001) were associated with better CAO response, while the presence of CAO response (p< 0.001) and BED10 ≥39 Gy (p= 0.008) were the factors to relate with better OS on multivariate analyses. The EBRT proves effective and durable CAO palliation with only 19.0% re-CAO rate in MLC patients. Better CAO responses may be achieved in patients treated with smaller tumor size, small-cell histology, and higher BED10 values.

Keywords: Central airway obstruction, Metastatic lung cancer, External beam radiotherapy

ÖZET

Akciğer Kanseri İlişkili Santral Hava Yolu Tıkanıklığı: Radyoterapiden Kim Daha Fazla Fayda Görür?

Metastatik akciğer kanserine (MAK) bağlı gelişen santral hava yolu tıkanıklığının (SHT) palyatif tedavisinde radyoterapinin (RT) etkinliği ve etkinlikle ilişkili faktörlerin araştırılması amaçlanmıştır. Bu amaçla 72 hasta geriye dönük olarak incelenmiştir. RT'ye cevap değerlendirmesi seri akciğer grafileri (SAG) kullanılarak yapılmıştır. Primer sonlanım noktası radyolojik cevap; ikincil sonlanım noktaları genel sağ kalım (GS), SHT'siz sağ kalım ve daha iyi sonuç göstergelerinin araştırılması olarak belirlenmiştir. RT dozları 8-40 Gy'dir (1-13 fraksiyon). Ortanca takip süresi ve GS sırasıyla 5.6 (aralık: 1.3-17.8) ve 7.6 (95% CI: 6.5-8.7) aydır. SAG ile takipte 58 (%80.6) hastada objektif yanıt elde edilmiş olup SHT'deki maksimum düzelme ortanca 23 günde (3-86) gerçekleşmiştir. RT'ye yanıt veren hastalardaki ortanca 8.3 aylık GS süresinin 8.1 ayında amaçlanan palyasyon sağlanırken; hastaların %19'da SHT tekrarlamıştır. Ortanca GS süresi RT'ye yanıt veren (8.3 karşın 2,4 ay; p< 0.001) hastalarda daha yüksek bulunmuştur. Küçük hücreli histoloji (p= 0.002), tümör boyutunun <5.3 cm (p= 0.007) ve biyolojik eşdeğer dozun ≥39 Gy (p< 0.001) olması RT sonrası SHT'de daha iyi yanıtla ilişkili bulunurken; çok değişkenli analizlerde RT'ye yanıt (p< 0.001) ve BED10 ≥39 Gy (p= 0.008) daha uzun GS ile ilişkili bulunmuştur. RT ile MAK'da gelişen SHT'de etkin ve uzun süreli palyasyon sağlanmıştır (sadece %19'luk SHT'de tekrarlama). Tümör boyutu küçük olan, küçük hücreli alt histolojiye sahip ve yüksek doz RT uygulanan (BED10) hastalarda SHT'de daha iyi sonuçlar elde edilebilir.

Anahtar Kelimeler: Santral hava yolu tıkanıklığı, Metastatik akciğer kanseri, Eksternal beam radyoterapi

INTRODUCTION

Central airway obstruction (CAO), defined as obstruction of the lumen or air flow at the level of trachea, main carina and main bronchi due to intra- or extraluminal disease is one of the major complications of locally advanced- and metastatic lung cancer (MLC) which deteriorates patients' quality of life (QoL) measures and survival outcomes. CAO may develop in nearly up to 30% lung cancer patients either at the early phases or later anywhere during the disease course.[1,2]

Although the well-established initial management of MLC constitutes systemic chemotherapy, yet persistent symptoms related with CAO may mandate the urgent use of invasive or/and non-invasive interventions against primary obstructive area as the initial step of treatment.[3,4] In these situations, the commonly utilized treatment modalities involve the stent placement, dilatation, endoscopic laser ablation (ELA), argon plasma coagulation (APC), photodynamic therapy (PDT), endobronchial brachytherapy (EBB) and external beam radiotherapy (EBRT).[5-7] In general, ELA, APC, PDT, and EBB are implemented for the treatment of intraluminal tumors, while stent placement is usually reserved mainly for the obstructions caused by extraluminal masses with/without intraluminal extensions.[8] Aside the technical difficulties in their use, almost each of these modalities has the potential to cause severe complications; such as, fatal hemorrhage and lower respiratory tract infections for airway stents[9-12] or tracheobronchitis, hemoptysis, tracheomalacia and bronchial stenosis for EBB[8], which frequently precluding their use as the first maneuver for CAO palliation. These severe complications may underlie the obvious need for alternative noninvasive but efficient treatment modalities with minimal toxicity profiles.

Considering its well-recognized tumor downsizing and palliative efficacy irrespective of the tumor's relation with bronchial lumen, together with its noninvasive characteristic and minimal toxicity profile EBRT appears to be a suitable candidate for CAO palliation.[8] Therefore, in scarcity of such studies, we planned to retrospectively assess the efficacy of palliative EBRT and associated prognostic factors in MLC patients presenting with clinical symptoms or chest X-ray findings of CAO.

PATIENTS and METHODS

Eligibility Criteria

A retrospective database search was performed to identify MLC patients presenting with clinical symptoms or chest X-ray findings of CAO. To be eligible, patients had to meet the following criteria: histologically proven non-small cell- (NSCLC) or small-cell lung carcinoma (SCLC) diagnosis; age >18; Eastern Cooperative Oncology Group (ECOG) performance of 0-3; available pre- and post-EBRT chest X-rays, available EBRT dosimetric datasets, and no history of prior thoracic radiotherapy (RT) to the apparent CAO port. The study protocol was approved by the institutional review board before any data collection.

Radiotherapy

Patients underwent volumetric treatment planning computerized tomography (CT) scan using wing board in the treatment position. The gross tumor volume (GTV) solely included the apparent mass on computerized tomography which was judged to cause CAO. The available 18F-flourodeoxyglucose (FDG)-positron emission tomography was utilized in cases with accompanying atelectasis in order to discriminate from the tumor. According to our institutional standards for such patients the clinical target volume (CTV) was equivalent to GTV, while the planning target volume (PTV) was created by adding an isometric 1 cm margin to the CTV at all directions. The right, left and total lungs, heart, spinal cord (SC), esophagus and whole liver were all delineated as the organs at risk (OAR). Total doses of 8 to 40 Gy in 1 to 13 fractions were prescribed and 3-dimensional conformal EBRT technique was utilized in all patients. The optimal EBRT schedule was chosen by taking into account the performance status of patient, tumor size and proximity with the OAR. To be acceptable, the 95% isodose line had to cover the 100% of the PTV and maximal PTV dose was restricted to 107% of the prescribed dose. In case of using the 39-40 Gy schedules in 13 and 10 fractions, respectively, the maximum dose constraint of spinal cord was calculated utilizing the biologically equivalent dose-2 Gy (BED2= n.d.(1+d/α/ß), with 36.6 Gy and 30.6 Gy maximum point doses being set for 39 and 40 Gy, respectively. Concurrent chemotherapy was not permitted.

Table 1. Patient baseline and treatment characteristics

Characteristics	All patients
Median age, years (range)	64 (46-79)
Gender (N;%)	
Male	52 (72.0)
Female	20 (28.0)
ECOG performance (N;%)	
1	36 (50.0)
2	18 (25.0)
3	18 (25.0)
Histology (N;%)	
NSCLC	53 (73.6.0)
SCLC	19 (26.4.0)
EBRT schedule (N;%)	
1 x 8 Gy	7 (9.8)
5 x 4 Gy	13 (18.0)
10 x 3 Gy	30 (41.7)
12 x 3 Gy	5 (7.0)
13 x 3 Gy	13 (18.0)
10 x 4 Gy	4 (5.5)

ECOG, eastern cooperative oncology group; NSCLC, non-small cell lung carcinoma; SCLC, small-cell lung carcinoma; EBRT, external beam radiotherapy; Gy, gray

Response Assessment

The obstructive symptoms and treatment related acute toxicity were assessed every week or more frequently when necessary during the treatment. Revealed from the cohorts any symptom scoring systems or patient-reported questionnaires were not utilized. Therefore, the symptomatic response was assessed subjectively and solely by depending on the patients' verbal response at each meeting with the best verbal response being the best symptomatic response date. After the treatment, patients were first monitored at monthly intervals for the first 3 months and at 3-month intervals or more frequently thereafter. The objective response was assessed by comparison of the chest X-rays which were obtained prior and following the treatment.

Statistical Analysis

The primary end-point of the present study was the radiologic CAO response rate to EBRT. The secondary end-points were survival outcomes, namely overall survival and median CAO-free survival which were defined as the interval between the first EBRT day and the date of death/last visit and the date of lung re-obstruction, respectively. Survival was analyzed by using the Kaplan-Meier method. In order to determine the potential impact of continuous variables on survival and CAO response rates, Receiver Operating Curve (ROC) was utilized to categorize patients into groups according to the defined cut-off values, if available. The survival curves of subgroups were compared by using two-sided log-rank tests. A cox proportional hazard model was utilized for analyzing the relationship between different variables and survival. All tests were two-tailed. A p-value ≤ 0.05 was considered significant. For the assessment of the potential correlation between CAO response to EBRT and available covariates, the Spearman Analysis was utilized with related P (rho) values. All the delivered doses were converted to BED10 to perform more reliable comparison and analysis between the treatment schedules.

RESULTS

A total of 72 MLC patients with CAO were identified to be treated with palliative EBRT at our institution and included in this retrospective cohort analysis. Patient and treatment characteristics were as summarized in Table 1. Median age was 64 years (range: 46-79) with 72% being male and 75% having ECOG 0-2. Median EBRT dose was 30 Gy (range: 8-40) which was administered in 10 fractions (range: 1-13).Treatment was relatively well tolerated with only 5 (6.9%) acute grade 3 toxicities (4 pneumonitis and 1 esophagitis) and no report of late grade 3-5 toxicity.

Although 11 (19.0%) later developed re-CAO at somewhere during the follow-up period, resolution of CAO to some degree was reported in 58 patients (80.6%) on serial chest X-ray examinations either during or after the completion of EBRT with no notable response in remaining 14 (19.6%). The median time to achievable maximum expansion of the obstructed lung was 23 days (range: 3-86) from the initiation date of EBRT for the responders which remained durable for a median of 8.1 months (95% CI: 3.7-12.5). Time to maximum CAO response

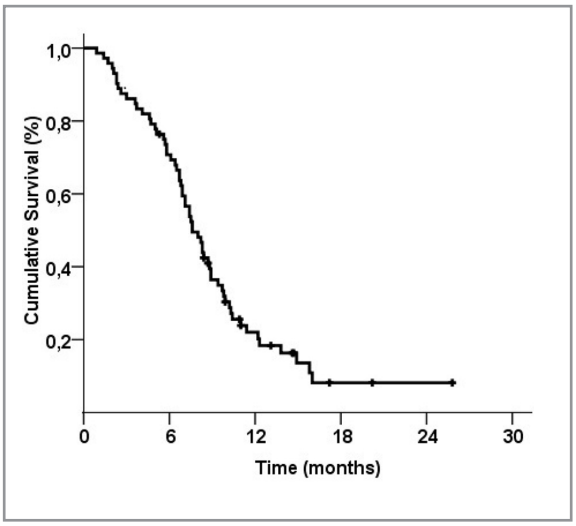

Figure 1. Overall survival in all patients

was significantly shorter in the SCLC than the NSCLC cohort (5 vs. 28 days; p= 0.02). Similarly, maximum CAO response rate was also significantly higher in SCLC patients (89.5% vs. 77.3%; p= 0.02).

At a median follow-up of 5.6 months (range 1.3-17.8), the median OS and CAO free survival were 7.6 (95% CI: 6.5-8.7) and 7.2 months (95% CI: 6.0-8.5) for the entire study population, respectively (Figure 1). The patients with CAO response had significantly longer median OS (8.3 vs. 2.4 months; p< 0.001) than the non-responders (Figure 2). For the 11 patients who experienced re-CAO had 7.4 and 5.2 months median OS and CAO-free survival times, respectively. The median (8.3 vs. 6.4 months; p= 0.014) and 1-year (26.9 vs. 10.9; p< 0.001) OS rates were prominently higher in patients receiving BED10 doses ≥39 Gy than the lower dose counterparts (Figure 2).

In correlation analysis by Spearman test revealed that the smaller tumor size (<5.3 vs. ≥5.3 cm; p= 0.007) defined by ROC analysis, higher BED10 dose (≥39 vs. 39 Gy; p< 0.001) and SCLC histology (SCLC vs. NSCLC; p= 0.002) were determined to be the factors to associate with better CAO response rates (Table 2). Univariate analysis assessing the OS outcomes indicated that smaller tm size (< 5.3 cm; p= 0.04), higher EBRT dose (BED10 ≥39 Gy; p<0.001) and CAO response (present; p<0.001) were the factors to associate with significantly superior median OS times (Table 3). However, multivariate analysis including only these

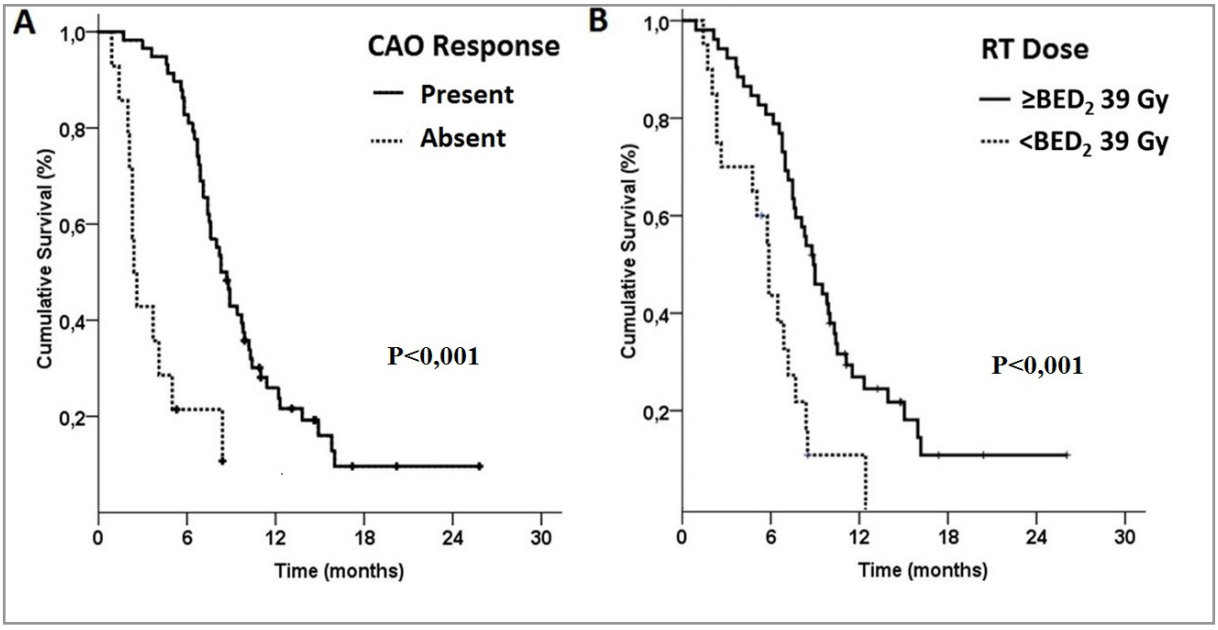

Figure 2. (A) Overall survival according to the central airway obstruction status (CAO) **(B)** Overall survival according to the biologically equivalent dose-10 Gy (BED10)

Table 2. Outcomes of Spearmen analysis for determinants of CAO response

Characteristic	Patients N (%)	Response Rate (%)	Correlation Coefficient (Rho-value)	p
Gender				
Male	52 (72.2)	80.7	-0.009	0.94
Female	20 (27.8)	80.0		
ECOG				
0-1	36 (50.0)	77.0	0.033	0.78
2	18 (25.0)	86.6		
3	18 (25.0)	81.3		
Tumor histology				
SCLC	53 (74.0)	89.5	0.135	0.002
NSCLC	19 (26.0)	77.3		
Tumor size				
< 5.3 cm	42 (58.3)	92.8	-0.355	0.007
≥ 5.3 cm	30 (41.7)	63.3		
BED10 (Gy)				
≥ 39 Gy	20 (27.7)	90.3	0.400	<0.001
< 39 Gy	52 (72.3)	55.0		

ECOG: eastern cooperative oncology group; SCLC: small-cell lung carcinoma; NSCLC: non-small cell lung carcinoma; BED: biologically equivalent dose; Gy: gray;

three factors demonstrated that the tumor size lost its significant association with OS outcomes leaving the higher EBRT dose and presence of CAO response as the associators of longer OS (Figure 2).

DISCUSSION

The results of this present retrospective analysis in 72 MLC patients with CAO demonstrated that the EBRT efficiently palliated the CAO in 80.6% patients for a relatively durable time period (8.1 months) compared to their short life span (8.3 months) with only 19.0% CAO recurrences in the responders. Additional analysis revealed a significant and independent association with better CAO response and longer survival in patients with SCLC histology and EBRT dose of BED10 ≥39 Gy. Present results also showed that the smaller tumor size, SCLC histology, and BED10 ≥39 Gy were associated with higher CAO response rate, while longer survival was appeared to relate to presence of CAO response and BED10 ≥39 Gy EBRT dose, respectively.

Progressive local/regional tumor growth in MLC patients may lead to significant suffering from dyspnea, hemoptysis, and cough either of which may mandate urgent palliative interventions such as stent placement, ELA, and/or PDT.[13,14] Obviously, these invasive treatment modalities are satisfactorily effective in terms of providing rapid palliation in patients with CAO. However, to be applicable, first the tumor should allow the installation of the stent which may be quite difficult for endobronchial tumors obstructing the lumen near totally. Moreover, stent migration and/or obstruction are additional potential problems to be overcome that may either limit their frequent usage or may indicate use of further palliative interventions. Similarly, EBB is another invasive technique with favorable palliation outcomes for CAO. However, great caution is needed for interpretation of the EBB studies as most eligible patients had intrabronchial small tumors without extrinsic components. Alike with the aforementioned techniques EBB also suffers from a variety of notable complications including the esophageal-bronchial fistula,

Table 3. Results of univariate and multivariate analysis

Characteristic	Patients N (%)	Median Survival (months)	Univariate p-value	Multivariate p-value
Gender				
Male	52 (72.2)	7.4	0.13	–
Female	20 (27.8)	9.4		
ECOG				
0-1	36 (50)	8.0	0.48	–
2	18 (25)	7.6		
3	18 (25)	6.7		
Histology				
NSCLC	53 (74)	7.3	0.69	–
SCLC	19 (26)	8.6		
Tumor size				
< 5.3 cm	42 (58.3)	8.3	0.04	0.37
≥ 5.3 cm	30 (41.7)	6.8		
BED10 (Gy)				
< 39 Gy	20 (27.7)	5.8	<0.001	0.008
≥ 39 Gy	52 (72.3)	8.8		
CAO response				
Present	58 (80.5)	8.3	<0.001	<0.001
Absent	14 (19.5)	2.4		

ECOG, eastern cooperative oncology group; Gy, gray; NSCLC, non-small cell lung carcinoma; SCLC, small-cell lung carcinoma; EBRT, external beam radiotherapy CAO, central airway obstruction; BED, biologically equivalent dose

bronchial wall necrosis, and/or massive hemoptysis.[8,15-18] Considering these facts, the noninvasive EBRT with its minimal toxicity profile may be a rational treatment choice in these highly fragile patients with tumors of any size independent of their relation with the bronchial lumen.

One important finding of the present study was the excellent response rate of CAO to EBRT (80.6%) with relatively long CAO-free duration (8.1 months) compared to the median OS of 8.3 months achieved in the responder patients. This observation clearly underlies the long lasting efficacy of EBRT in management of CAO. Considering the efficacy of EBRT in management of CAO, in a study by Lee et al. including 95 patients who were treated with 8 to 45 Gy (1 to 15 fractions) EBRT due to obstructive lung masses of NSCLC (n= 59) or SCLC (n= 36) were analyzed.[19] The reported 79% CAO improvement with EBRT by Lee et al. is almost identical to our 80.6% response rate noted here. The present results are additionally confirmed by the reported 65-77% CAO improvement rate noted in the large Fairchild meta-analysis that included 13 randomized studies and 3473 patients.[20] Apart from this finding, we additionally demonstrated that even in the 11 patients (19%) who experienced re-obstruction after EBRT had a CAO-free interval of 5.2 months, corresponding to the 70% of calculated remaining life span (7.4 months) in these patients. This additional observation may serve important considering the detrimental effects of CAO on patients' quality of life and its appreciable improvement with EBRT.

In spite of the well-recognized differential efficacy of EBRT on local tumor control in non-metastatic SCLC and NSCLC patients[21,22], to our best knowledge, the tumor histology (NSCLC vs. SCLC) related CAO-response differences have been rarely addressed.[19] For instance, in their aforementioned study Lee et al. could not demonstrate any difference between the CAO responses of NSCLC and SCLC patients (78.0% vs. 80.6%; p= 0.76) after

EBRT.[19] In this respect our results are in stark contrast with Lee's outcomes as SCLC patients appeared to demonstrate better CAO response to EBRT (89.5% vs. 77.3%; p= 0.002). Although it is difficult to assign this distinction to exact causes, yet it is reasonable to anticipate that the striking higher radiosensitivity of SCLC to RT than NSCLC may have played the major role on this difference.[23] This anticipation is supported by the RT doses utilized in the landmark SCLC and NSCLC studies for non-metastatic LC patients [24-26], which is 45 Gy for SCLC [26] and 60-66 Gy for NSCLC.[24,25], respectively. Similarly, align with the related literature the faster maximum CAO-response observed here in SCLC patients than their NSCLC counterparts (5 vs. 28 days; p= 0.02) is also highly probable to associate with the higher relative radiosensitivity of the SCLC.[22]

In addition to better symptom improvement, high dose RT rather than the conventional palliative dose schedules may also prove survival benefit in patients presenting with CAO.[19,20,27] In line with this evident dose-response relationship [20], our analysis demonstrated that both the actual CAO resolution- (90.3 vs. 55%; p< 0.01) and median- (8.3 vs. 6.4 months; P=0.014) and 1-year (26.9 vs. 10.9%, p< 0.001) OS rates were significantly superior with BED10 doses ≥39 Gy than the lower dose counterparts. This observation is strengthened with a recent study by Tanaka et al.[27] and a relatively older meta-analysis by Fairchild et al.[20] In both analyses the authors reported a dose benefit of EBRT was also supported by and a study of which addressed to 35 Gy10 as a threshold value for prolonged survival (27% vs. 22% at 1-year; p= 0.002) and favorable symptom control, respectively. Therefore, altogether these results suggest the use of total dose and fractionation achieving for better results.

In addition to the tumor histology and EBRT dose, the tumor size is another suggested factor to alter CAO response rates after both EBB and EBRT.[2,19,28] Based on the available literature, it may be rational to propose that CAO caused by smaller tumors may response to a prescribed EBRT dose than larger ones, as it is evident from LC literature.[29] In this respect, tumor size of <6 cm was reported to associate with better CAO-free[19] and local control rates [30]. Similarly in our present study, the ROC analysis identified that patients with <5.3 cm tumor size as the cut off for better RT response (92.8 vs. 63.3%; p= 0.007) and median CAO-free interval (8.3 vs. 5.7 months; p= 0.012), this could not translate into a significant covariate affecting the outcomes in the multivariate analysis (p= 0.41). Therefore, the outcomes of Tanaka's study and the one presented here suggest a potential role for tumor size in prediction of CAO-response after EBRT, which deserve to be addressed in larger studies to conclude in a more reliable manner.

The present study has several drawbacks. First, as common to any single institutional small retrospective study, unpredictable biases may have influenced our results. Second, absence of the patient-reported objective questionnaire forms and functional examinations including respiratory function tests or bronchoscopic evaluations limit our ability to conclude more reliably. Instead, we utilized serial chest X-rays, patients' self-assessments, and physician in charge's judgement based on the physical examinations which are prone to biasing effects as they are more or less subjective evaluation tools. However, although we recognize the handicaps of subjective assessments, it should be remembered that use of more objective tools such as the respiratory function tests or CT scanning may be extremely difficult or even impossible in at least some patients with severe dyspnea. Fourth, use of different EBRT dose fractionation schedules in discretion of the physician in charge by considering the patients' general health status may have favored one group over the other, particularly the high dose group. In this respect, the dose response relationship in different performance status levels and its translation to survival outcomes in such patients deserves to be addressed in future studies with larger cohorts. And fifth, use of various chemotherapeutics and/or targeted agents in some patients may have potentially altered the outcomes reported here. Therefore, respecting these limitations, we believe that our results should better be interpreted with caution considering the above mentioned factors.

CONCLUSION

The outcomes of current retrospective analysis demonstrated efficacy of the EBRT in palliation of the NSCLC or SCLC originated CAO for almost the rest of their remaining life span in responders, with only 19.0% CAO recurrences. Additionally we identified the higher EBRT dose (BED10 ≥39 Gy), smaller tumor size (<5.3 cm) and SCLC histology as the factors to associate with better CAO response after the noninvasive EBRT.

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