

Quality of Life after endobronchial intervention of malignant central airway obstruction

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Key words:

- Central Airway Obstruction
- Interventional Bronchoscopy
- Lung Cancer
- Quality of Life

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SUMMARY

BACKGROUND: Patients with malignant central airway obstruction (mCAO) may need endobronchial intervention for symptoms relief (dyspnea, hemoptysis, post-obstructive pneumonia), but also to manage atelectasis and consequent respiratory failure that does not allow their treatment to continue. Quality of life (QoL) has been closely linked with symptom intensity in lung cancer patients. It is therefore important to relieve respiratory distress and inform patients, especially those who receive palliative care, about the benefits of an eventual endobronchial intervention. **METHODS:** Over an 18-month period, we enrolled 29 patients with symptomatic malignant central airway obstruction in order to re-establish airway patency. QoL and dyspnea were evaluated by the EORTC -C30 and EORTC -LC13 Questionnaire before the intervention, 1 week after and every following month until first relapse or death. **RESULTS:** Overall, 44.8% of patients (n=13) had poor Performance status (PS ≥ 3) and 51.7% (n=15) of patients were stage IV disease. QoL improved significantly from the first week up to the 6th month ($p < 0.05$). Global Health Questionnaire improved from 29.6 (Standard deviation=19.2) to 70.8 (SD=30.5) ($p < 0.05$) on week 24. Dyspnea assessed with EORTC-LC13 questionnaire decreased from 73.2 (SD=29.2) to 23.6 (SD=26) ($p < 0.05$) on week 24. Patients with PS ≥ 3 and those at stage IV had greater improvement. Benefits were seen independent of histology of malignancy or history of post-obstructive pneumonia. Mean time until first relapse was 21.2 weeks (SD=20.5) (n=6 patients) and time until death was 15.1 weeks (SD=7.9) (n=16 patients). Patients treated with chemotherapy before the intervention and those with stenosis of trachea and left main bronchus had worse survival. **CONCLUSIONS:** Interventional management of patients with mCAO results in sustained significant improvement of QoL and shortness of breath and should be considered as essential component of multidisciplinary cancer care approach. *Pneumon 2018, 31(4):212-220.*

BACKGROUND

It has been estimated that 30% of lung cancer patients develop dyspnea due to malignant central airway obstruction (mCAO) and its complications.^{1,2} In these cases, interventional therapeutic bronchoscopy remains an important method for airway management. Symptoms like dyspnea, hemoptysis and complications like obstructive pneumonia and atelectasis deteriorate patient's QoL and survival. Due to respiratory failure and sepsis patients who remain untreated are poor candidates for combined chemo-radio therapy. As a result, they report worse survival which commonly ranges from 1-2 months.³

In most cases endoscopic treatment has palliative effects since about 80% of patients are not candidates for radical surgical treatment. It is therefore important that every intervention improves QoL, dyspnea and physical performance and does not merely prolong patient's suffering.

Prior studies of therapeutic bronchoscopy for mCAO have shown statistically significant improvement of dyspnea the first month after intervention.^{5-8,14,17} Moreover, there is a positive impact on spirometry measurements like FEV₁.^{11,14,17} However, only one study shows sustained benefit on QoL over 2 months after the intervention.⁶

Endoscopic management of mCAO does not only have an impact on QoL but also on individual's survival.^{6,15,16} A brief review of the literature reveals that patients with mCAO treated endoscopically and with combined chemo-radio therapy had the same survival as patients of the same stage but without mCAO when treated with combined chemo-radio therapy.^{15,16} On the contrary, patients who remained untreated for mCAO survived only 1-2 months³. According to Stratakos Gr. et al. study, patients who denied endobronchial management had 2,93 times less likelihood of survival⁶.

We aimed to study the improvement of the overall QoL and of symptoms like dyspnea in a new well-defined population with patients of different stages of lung cancer, in order to review the efficacy of the interventional management of the central airways and to identify prognostic factors of better or worse outcome.

METHODS

The goal of this prospective study was to assess the effect of therapeutic bronchoscopic interventions when added to the standard oncologic treatment in patients with mCAO. The study was performed at "Sotiria" Athens

Chest Diseases Hospital after approval of the hospital's ethical committee. Patients were enrolled over a period of 12 months while the total follow up time was 18 months. Primary objectives included assessment of QoL and dyspnea before and after endoscopic intervention. Secondary objectives were time until first relapse, survival and identification of clinical, demographic and endoscopic characteristics that affect the outcome.

Subjects

All patients referred for interventional bronchoscopy were diagnosed with endobronchial obstruction due to primary lung cancer or metastatic cancer. Central airway obstruction was defined as occlusion of >50% of the trachea or main bronchus. Patients with poor performance status and low life expectancy were also included in the study. Patients with severe cardiopulmonary compromise and bleeding disorders were excluded. All patients signed consent form before enrollment.

Interventional Bronchoscopic procedures

The endoscopic team could choose the most appropriate method to reestablish airway patency based on each case using combination of different techniques when required. The procedure could include flexible or rigid bronchoscopy combined with electro-cryotherapy, mechanical debulking, Argon Plasma Coagulation and metal or silicon stent placement. Technical success was defined as reopening of the airway lumen to >50% of normal diameter.

Quality of Life assessment

QoL was assessed using a 30-point core questionnaire designed by the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire for Cancer (EORTC QLQ-C30, version 3) combined with the lung cancer specific module (LC-13). Dyspnea was assessed with both questionnaires EORTC QLQ-C30 and LC-13. All patients were evaluated before the intervention, 1 week after and every following month until first relapse or death.

The EORTC QLQ-C30 and LC13 are the most frequently used and well documented questionnaires in European countries^{10,12}. They have been used and validated in over 3000 studies globally^{4,9}. QLQ-C30 is composed of multi-item scales: 2 global QoL scales (Global Health Status score-GHS), 5 functioning scales (physical, role, emotional, cognitive, and social), and 3 symptom scales

(fatigue, pain, and nausea/vomiting). For the 5 functioning scales and the global QoL scale, a higher score represents better functioning. For the symptom scales and items, a higher score corresponds to a higher level of symptoms.

Statistical Analysis

The effect of variables recorded before endoscopy on the time of death / relapse, was quantified by a survival analysis model. Single and multivariate analysis was performed both for the time of death and for selected physical / mental health items of the questionnaire. Analysis used a 5% significance level and was performed using the R statistical packet for Windows (version 3.5.0).

RESULTS

During the 18-month period of the study 29 patients were enrolled. The intervention was considered successful in all patients as >50% of airway patency was achieved. Overall, 75.9% (n=22) of patients had primary lung cancer and 17.2% (n=5) had extrathoracic malignancy with endobronchial metastasis. The most frequent occlusion site was the right main bronchus in 58.6% (n = 17) of cases, followed by the trachea in 41.4% of the participants (n = 12), and the left main bronchus in 34.5% of the patients (n = 10). The majority of the patients had obstruction in more than one site (62.1%). Stent placement was reported in 12 patients (41.4%).

Almost half of the patients (44.8%, n = 13) had PS ≥ 3 and half of them (51.7%, n = 15) had stage IV of disease. Moreover, 58.6% of patients (n = 17) were already treated with chemotherapy and 34.5% (n = 10) with radiotherapy. A combination of radio-chemotherapy was reported in 31% of the participants (n = 9), while 20.7% (n = 6) of them had no prior treatment. (Table 1)

Most QoL data improved significantly from the first week up to the 6th month after the intervention ($p < 0.05$) (Table 2). The Global Health Status (GHS) score improved from the initial score of 29.6 (SD = 19.2) to 70.8 (SD=30.5) on week 24 ($p < 0.05$) (Figure 1).

Dyspnea estimated with the EORTC-LC13 questionnaire was reduced from 73.2 (SD = 29.2) to 23.6 (SD = 26) on week 24 ($p < 0.05$) (Figure 2). Patients with PS ≥ 3 and those at Stage IV had worse scores before the intervention but showed the greatest improvement from the first month of follow up. The assumption that patients at advanced stage or poor PS do not benefit as much as lower-stage patients was not confirmed. The improvement was inde-

TABLE 1 Baseline characteristics of the patients.

Variable	N (%)	Mean
Sex (M)	21 (72.4)	
PS		
0	3 (10.3)	
1	9 (31.0)	
2	4 (13.8)	
3	8 (27.6)	
4	5 (17.2)	
Age	29.0	62.9 (SD=9.6)
Istology		
Primary Lung Cancer	22 (75.9)	
Metastasis	5 (17.2)	
Other	1 (3.4)	
Unknown	1 (3.4)	
Lung Cancer pathology		
NSCLC squamous	12 (54.5)	
NSCLCadenCa	8 (36.4)	
Trachea adenoid cystic carcinoma	1 (4.5)	
SCLC	1 (4.5)	
Position		
Trachea	12 (41.4)	
Right main bronchus	17 (58.6)	
Left main bronchus	10 (34.5)	
Stent	12 (41.4)	
Positions of obstruction		
1	11 (37.9)	
2	14 (48.3)	
3	4 (13.8)	
Stage (TNM)		
IV	15 (51.7)	
IIIB	8 (27.6)	
IIIA	4 (13.8)	
IB	1 (3.4)	
unknown	1 (3.4)	
Postobstructive pneumonia	15 (51.7)	
ChemoTherapy	17 (58.6)	
Xray Therapy	10 (34.5)	
Oxygen Therapy	12 (41.4)	
Chemo & Xray	9 (31.0)	
Therapy Count		
0	6 (20.7)	
1	11 (37.9)	
2	8 (27.6)	
3	4 (13.8)	
Smoking PY	29.0	61.2 (SD=44.4)
Comorbidities		
COPD	15 (51.7)	
Coronary disease	2 (6.9)	
No COPD/Coronary Disease/RenalFailure	12 (41.4)	

- Positions of obstruction: Concurrent obstruction sites in Trachea, Right main bronchus, Left main bronchus

- Number of therapies that preceded: Chemotherapy, Radiotherapy, Oxygen Therapy.

TABLE 2. Quality of Life (EORTC Q30 & LC13) prior to intervention and follow-up from 1st week and then every month up to 6th month.

Questionnaire	before	1 wk	4 wks	8 wks	12 wks	16 wks	20 wks	24 wks
	(n=29)	(n=28)	(n=26)	(n=21)	(n=20)	(n=11)	(n=10)	(n=8)
Global Health status	29.6119.2	65.5 ±14.3*	67.9± 16.8*	67.1 ±17.2*	67.9116.2*	71.2116.8*	70.0118.9*	70.8+30.5*
Functional - Physical	30.6125.8	58.8124.1*	65.1 +25*	65.4123*	67.0126.4*	63.6+31.6*	68.0+33.5	70.8+35.8
Functional - Role	21.3130.8	44.6128.7*	56.4+32*	55.6129.5*	62.5132.8*	53.0+40*	61.7141.6	68.8+39.3
Functional - Emotional	55.2130.7	75.9122.4*	77.2+23.9*	78.2122.3*	85.4116.2*	83.3+13.9	88.3+10.5	89.6+8.6
Functional - Cognitive	70.1130	80.4120.8*	80.1+21.6*	80.2119.5	84.2+17.5	89.4+15.4	91.7114.2	89.6+15.3
Functional - Social	37.9+30.8	57.7126.2*	62.8+26.4*	61.9128*	69.2119.7*	68.2+24.1	75.0118	79.2117.3
Symptom - Fatigue	72.0129.5	42.5124.8*	39.7126.9*	42.9+24.7*	35.6119.3	37.4121.2*	30.0118.9*	31.9128.8
Symptom - Nausea & Vomiting	12.1117.2	3.019.1*	5.8+16.3	7.9+19.5	5.8+12.4	4.5+10.8	0.0+0	0.010
Symptom - Pain	39.1+40.2	24.4+29.2*	25.0130.6*	26.2+31	18.3+21.6	13.6+22.1	8.3+14.2	12.5114.8
LC13 - Dyspnoea	73.2±29.2	38.1+19.7*	32.1123.8*	32.3120.8*	30.0124.7*	26.3122.4*	25.6+29.2	23.6126.2*
LC13 -Haemoptysis	39.1+41.9	9.5115.3*	5.1120.4*	0.010*	1.717.5*	0.0+0	0.0+0	4.2+11.8
LC 13 - Coughing	77.0+28.3	35.7+12.6*	32.1127.5*	31.7122.3*	31.7125.3*	27.3129.1*	23.3127.4*	20.8124.8*

*Values differ statistically significantly compared to pre-bronchoscopy values.

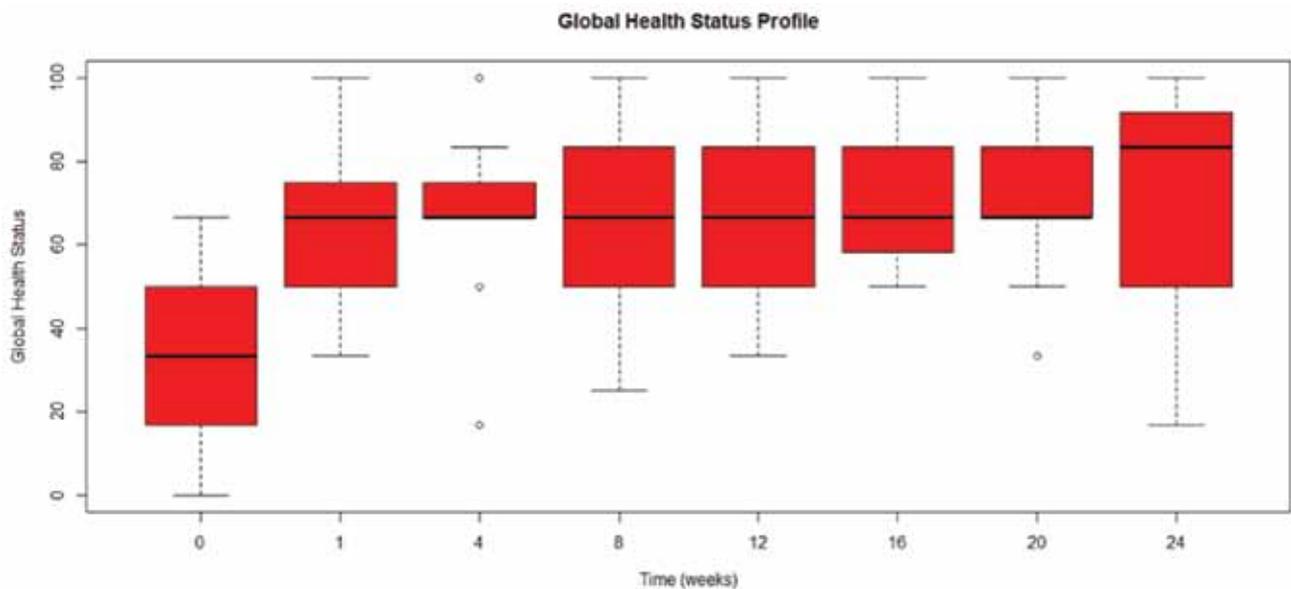


FIGURE 1. Global Health Status Questionnaire: Before invasive bronchoscopy and follow-up at 1st week and then every month until 6th month.

pendent of the histological type of malignancy and the history of post-obstructive pneumonia.

The mean follow-up time was 22.5 weeks (SD 9.6, median = 17, min = 0.1, max = 70 weeks). Overall, 16 patients died, 6 relapsed and new intervention was needed, 6 patients did not relapse until the study was completed, and one was missed during follow-up on 5th month. The

mean time until first relapse was 21 weeks (mean = 21.2 weeks, SD = 20.5), suggesting that for 5 months patients who suffocated or were at risk of infections had adequate time to receive the proper oncology treatment with improved daily QoL. Moreover, the median survival time was 3.5 months (mean = 15.1 weeks, SD = 7.9), longer than the expected 1-2 months survival in not interventionaly

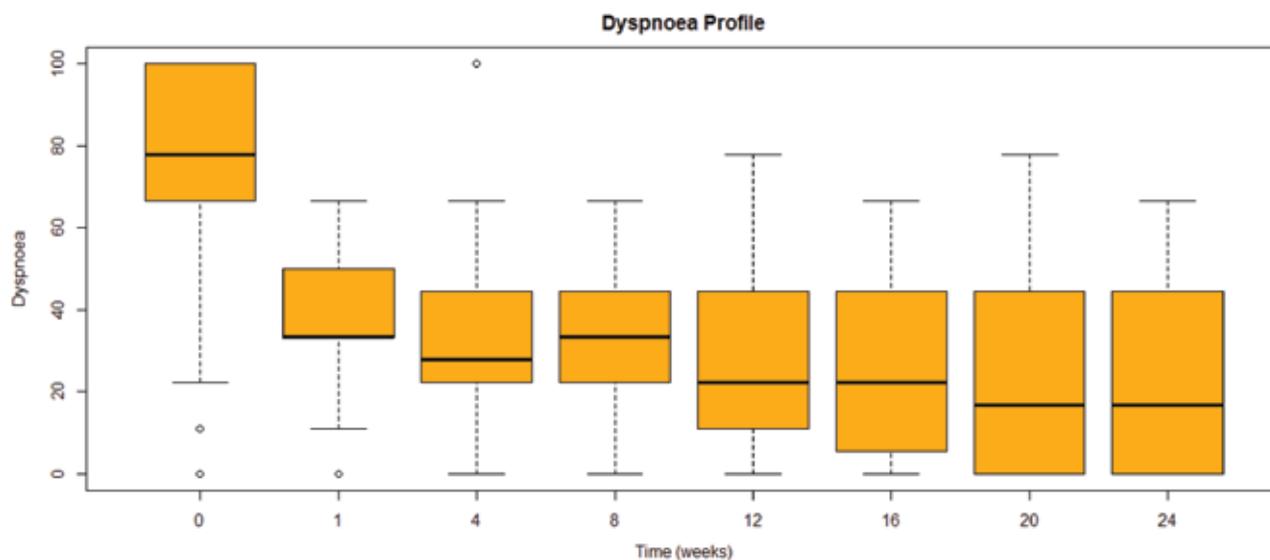


FIGURE 2. Dyspnea scale Questionnaire (EORTC LC-13): Before invasive bronchoscopy and follow-up at 1st week and then every month until 6th month.

treated patients according to the older study by Macha et al³ (Table 3).

Regarding the complications of invasive bronchoscopy, endobronchial bleeding occurred in one patient and was controlled with a new bronchoscopy the first 48 hours after intervention. Also, one patient with stent presented with MRSA pneumonia 6 months after the intervention and the stent was removed.

Since there is no control group to compare the time of relapse or death, an analysis of the patient characteristics that could affect that time was performed. Univariate analysis demonstrated that patients with PS ≥ 3 and those

already treated with chemotherapy had worse survival at 6 months. However, in the multivariate analysis, when all the features were studied simultaneously, PS was no more considered as a negative predictive factor (Table 4).

Analysis showed that tracheal obstruction increased the risk of death by 12.93 times ($p < 0.05$) (Figure 3). In addition, left main bronchus obstruction increased the risk of death by 7.65 times ($p < 0.05$) and the combination of tracheal and left main bronchus stenosis had the worst prognosis (Figures 4 and 5). A possible explanation could be that trachea obstructions are more critical for breathing impairment since trachea is the central airway

TABLE 3. Follow up and outcome (weeks).

Outcome	N(%)					
Death	16 (55.2)					
Relapse	6 (20.7)					
Without relapse*	6 (20.7)					
Lost to follow-up	1 (3.4)					
Follow-up Weeks	N(%)	Mean	SD	Median	Min	Max
Overall	29.0	22.5	17.1	17.0	0.1	70.0
Weeks to Death or Relapse	22.0	16.7	12.4	16.5	0.1	60.0
Weeks to death	16.0	15.1	7.9	16.5	0.1	30.0
Weeks to relapse	6.0	21.2	20.5	15.0	4.0	60.0
Without relapse or lost follow up*	7.0	40.7	17.7	43.0	17.0	70.0

* Follow up of patients without relapse stopped due to completion of study time

TABLE 4. Multivariate analysis: Factors that statistically affect survival.

Variable	HR	95% CI	p-value
Trachea	12.93	2.94-56.81	0.1%
Left main bronchus	7.65	2.14-27.28	0.2%
Chemotherapy	4.49	1.18-17.15	2.8%
Smoking PY	1.01	1.00- 1.03	2.2%

and even slightest stenosis may have a significant effect on the oxygenation. Furthermore, interventions in the left main bronchus are technically more demanding according to Ost et al⁵. Finally, the history of previous chemotherapy reduced survival by 4.49 times ($p < 0.05$) (Figure 6). Regarding the patients already treated with chemotherapy, it is likely that their tumor was more resistant to size reduction. On the contrary, treatment

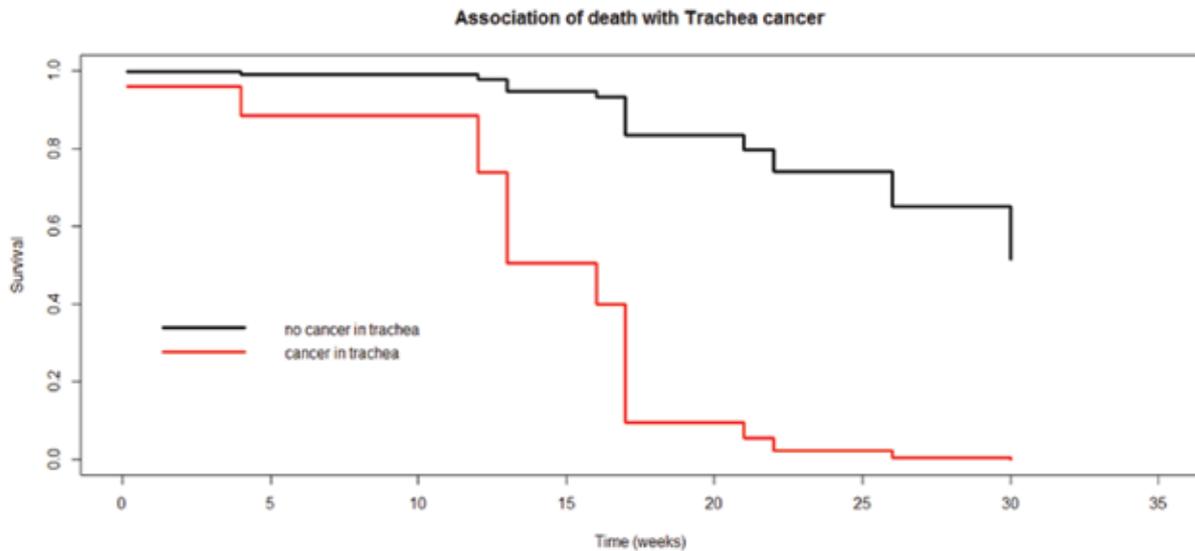


FIGURE 3. Multivariate analysis: Survival of patients with tracheal obstruction compared to those who did not have trachea obstruction (had only occlusion in the main bronchus).

* Conclusions should be carefully evaluated after 6 months (24 weeks) as the sample is small. The survival curves display data beyond 6 months.

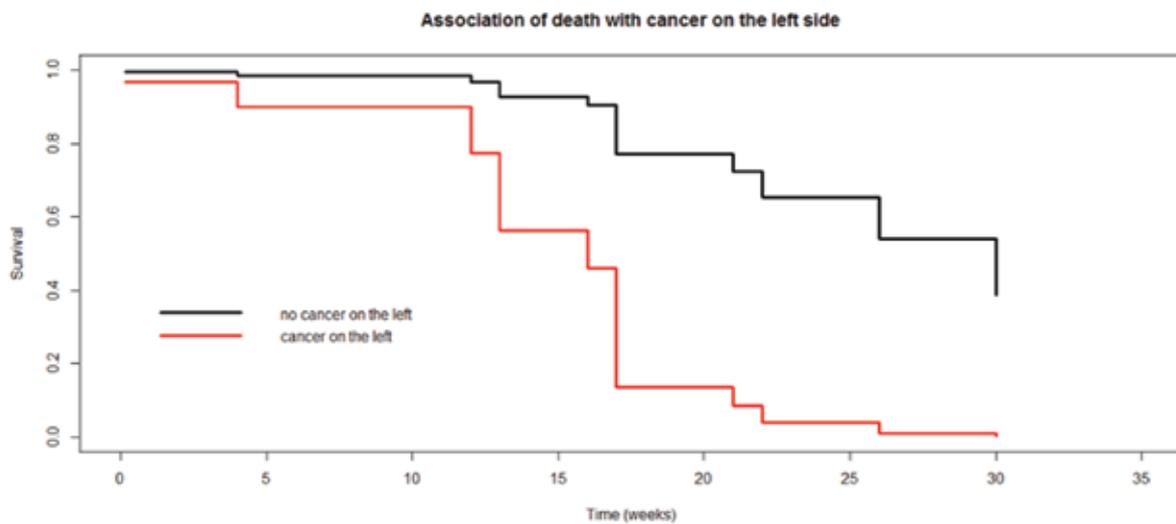


FIGURE 4. Multivariate analysis: Survival of patients with left main bronchus obstruction.

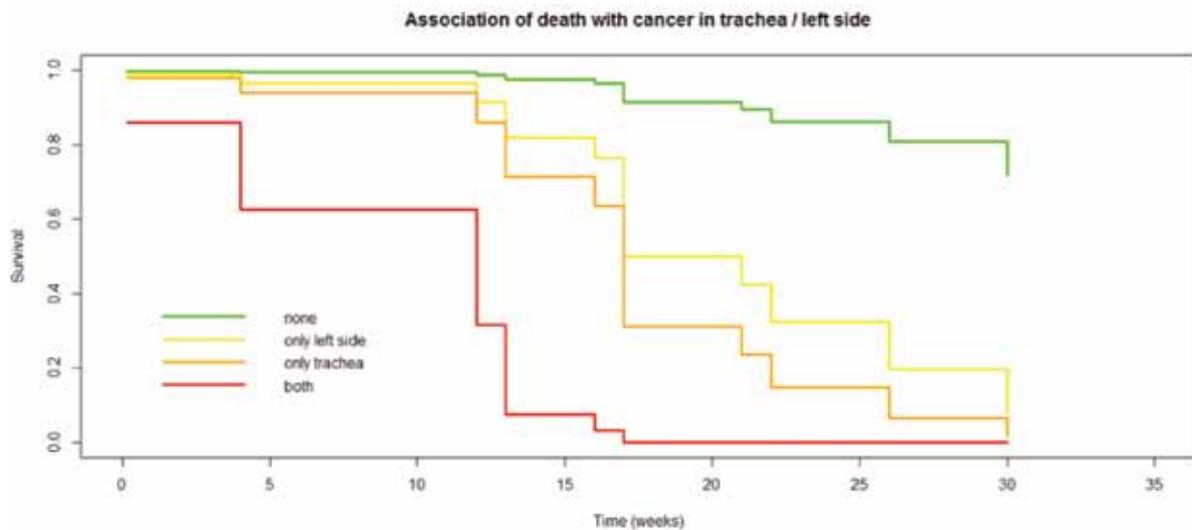


FIGURE 5. Multivariate analysis. Impact of obstruction site on survival. The combination of obstruction in the trachea and left main bronchus has the worst outcome in the follow-up period. Note: none = occlusion in the right main bronchus only.

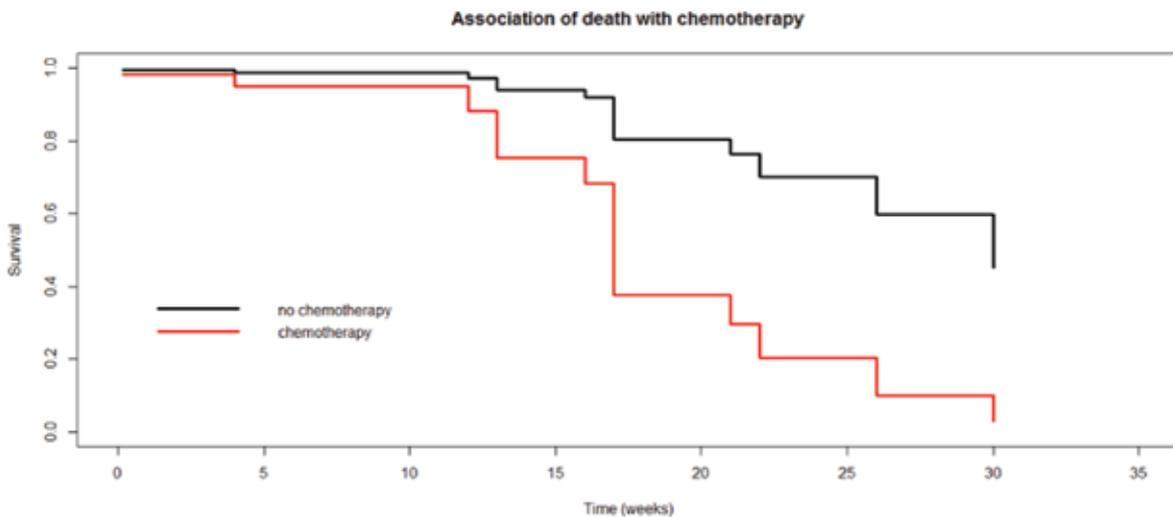


FIGURE 6. Multivariate analysis: Survival of patients who received chemotherapy before study enrollment.

naïve patients benefited from both the central airway opening and the additional effect of chemotherapy \pm radiotherapy. A similar result was reported by Kyeongman from a 5 years retrospective study.¹⁹ The stage of disease or the history of post-obstructive pneumonia were not found to affect the outcome.

This study has several limitations. First of all, it is a single reference center study and the cohort of patients ($n = 29$) is small, so extrapolation of the results to larger number of patients and bronchoscopic centers, is not safe. Another limitation is the coexistence of patients

with primary and metastatic extrathoracic lung cancer as the course of the disease is expected to differ. However, according to Mahmood et al. study, survival between the two groups was not affected.¹⁷ Moreover, the overall monitoring time was limited due to the initial study design and the statistical analysis included data from a 6-month follow-up. It is difficult to understand whether the improvement observed was only because of the endoscopic intervention or whether it was influenced by other types of concomitant therapy. Time was given though for chemotherapy and radiotherapy to work and

protect patients from complications such as suffocation, pneumonia and sepsis that are not necessarily related to the stage of the disease. Due to ethical reasons, no control group was included in our study as bronchoscopic intervention could not be denied to any patient with mCAO, thus no comparison could be made.

CONCLUSIONS

In this prospective study, we found a positive impact of therapeutic bronchoscopy on QoL and dyspnea scale values in patients with mCAO. This improvement was observed regardless of the type of malignancy causing the airway obstruction. Scores were significantly improved from the first week and remained so throughout the 6-month follow-up period. As the deterioration of respiratory symptoms is associated with worse QoL, decreased physical activity, reduced self-care ability and a significant reduction in social activities regardless of stage¹⁸, the emergence of this improvement has a significant impact on patient's decision to undergo an invasive procedure. The disease stage and poor PS, especially when this is

attributed to dyspnea, should not exclude patients from endoscopic intervention. Finally, although there was no control group, there is evidence that survival time is prolonged, as has been shown by other studies^{3,6}, but this should be carefully assessed. Multi-center studies with larger number of patients and longer follow-up period are needed.

It is important to recognize the necessity of invasive bronchoscopy and to ensure that specialized hospitals where complicated cases of lung cancer are treated and all large oncology units are familiar and have access to interventional endoscopic procedures. Interventional management of patients with mCAO results in sustained significant improvement of QoL and shortness of breath and should be considered as an essential component of the personalized multidisciplinary oncology care approach.

ACKNOWLEDGEMENTS

We would like to thank D. Lamprou Athens, Greece, for his valuable assistance in the statistical analysis and the presentation of the data of this study.

ΠΕΡΙΛΗΨΗ

Ποιότητα ζωής σε ασθενείς με καρκίνο πνεύμονα μετά τη διάνοιξη κεντρικών αεραγωγών

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Εισαγωγή: Οι ασθενείς με κακοήθη απόφραξη κεντρικού αεραγωγού έχουν ένδειξη επεμβατικής διάνοιξης για τη βελτίωση των συμπτωμάτων τους (δύσπνοια, αιμόπτυση, μεταποφρακτική πνευμονία) αλλά και για την άρση ατελεκτασιών και συνεπακόλουθης αναπνευστικής ανεπάρκειας που δεν επιτρέπει τη συνέχιση της θεραπείας τους. **Μέθοδοι:** Κατά τη διάρκεια 18 μηνών εντάχθηκαν στη μελέτη 29 ασθενείς, οι οποίοι αντιμετωπίστηκαν με επεμβατική βρογχοσκόπηση για διάνοιξη κακοήθους απόφραξης κεντρικού αεραγωγού. Η ποιότητα ζωής και η δύσπνοια αξιολογήθηκαν με τα προτυποποιημένα ερωτηματολόγια EORTC-C30 και EORTC-LC13 πριν την παρέμβαση, 1 εβδομάδα μετά και έπειτα κάθε μήνα μέχρι την πρώτη υποτροπή ή τον θάνατο. **Αποτελέσματα:** Το 44.8% των ασθενών (n=13) είχαν φτωχό Performance status (PS) (≥ 3) και το 51.7% (n=15) των ασθενών βρισκόταν στο IV στάδιο της νόσου. Η ποιότητα ζωής βελτιώθηκε στατιστικά σημαντικά από την πρώτη εβδομάδα παρακολούθησης και καθ' όλη τη διάρκεια του επόμενου 6μήνου. Το ερωτηματολόγιο Global Health Questionnaire βελτιώθηκε από 29.6 (SD=19.2) σε 70.8 (SD=30.5) ($p < 0.05$) την 24^η εβδομάδα. Η δύσπνοια (εκτιμώμενη με το EORTC-LC13) μειώθηκε από 73.2 (SD=29.2) στο 23.6 (SD=26) ($p < 0.05$) την 24^η εβδομάδα. Οι ασθενείς με PS ≥ 3 και αυτοί σταδίου IV είχαν τη μεγαλύτερη βελτίωση. Ο μέσος χρόνος μέχρι την πρώτη υποτροπή ήταν 21.2 εβδομάδες (SD=20.5) (n=6 ασθενείς) και ο μέσος χρόνος μέχρι το θάνατο ήταν 15.1 εβδομάδες (SD=7.9) (n=16 ασθενείς). Οι ασθενείς

με προηγηθείσα χημειοθεραπεία και όσοι είχαν απόφραξη στην τραχεία και τον αριστερό στελεχιαίο βρόγχο είχαν χειρότερη πρόγνωση. **Συμπέρασμα:** Η επεμβατική διάνοιξη σε ασθενείς με κακοήθη απόφραξη κεντρικού αεραγωγού βελτιώνει σημαντικά και σταθερά την ποιότητα ζωής και τη δύσπνοια και θα πρέπει να αποτελεί μέρος της σύγχρονης διατομεακής ογκολογικής αντιμετώπισης.

Πνεύμων 2017, 30(4):212-220.

Λέξεις - κλειδιά: Κεντρική απόφραξη αεραγωγού, Επεμβατική βρογχοσκόπηση, Καρκίνος πνεύμονα, Ποιότητα ζωής

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