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Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE) / Marchioni, A., Andrisani, D., Tonelli, R., Piro, R., Andreani, A., Cappiello, G.f., Meschiari, E., Dominici, M., Bavieri, M., Barbieri, F., Taddei, S., Casalini, E., Falco, F., Gozzi, F., Bruzzi, G., Fantini, R., Tabbì, L., Castaniere, I., Facciolongo, N., Clini, E.. - In: LUNG CANCER. - ISSN 0169-5002. - 148:(2020), pp. 40-47. [10.1016/j.lungcan.2020.07.032]

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07/06/2026 20:40

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Lung Cancer

Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE)

--Manuscript Draft--

Manuscript Number:	LUNGCANCER-D-20-00885R1
Article Type:	Research paper
Keywords:	Non-small cell lung cancer; central airway obstruction; therapeutic bronchoscopy; mechanical debulking; airway stent; KRAS-mutant tumors
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Abstract:	Objectives Despite new therapeutic perspectives, the presence of central airways occlusion (CAO) in patients with locally advanced non-small cell lung cancer (NSCLC) is associated with poor survival. There is no clear evidence on the clinical impact of interventional bronchoscopy as a part of an integrated treatment to cure these patients. Materials and methods This retrospective cohort study was conducted in two teaching hospitals over a 10 years period (January 2010-January 2020) comparing patients with NSCLC at stage IIIB and CAO at disease onset treated with chemotherapy/radiotherapy (standard therapy-ST) with those receiving interventional bronchoscopy plus ST (integrated treatment-IT). Primary outcome was 1-year survival. The onset of respiratory events,

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	symptoms-free interval, hospitalization, need for palliation, and overall mortality served as secondary outcomes. Results A total of 100 patients were included, 60 in the IT and 40 in the ST group. Unadjusted Kaplan-Meier estimates showed greater effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003). IT showed a significantly higher survival gain over ST in those patients showing KRAS mutation (7.6 VS 0.8 months,<0.0001), a lumen occlusion >65% (6.6 VS 2.9 months,<0.001), and lacking the involvement of left bronchus (7 VS 2.3 months,<0.0001). Compared to ST, IT also showed a favorable difference in terms of new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01). Conclusions In patients with NSCLC stage IIIB and CAO, additional interventional bronchoscopy might impact on 1-year survival. Genetic and anatomic phenotyping might allow identifying those patients who may gain life expectancy from the endoscopic intervention.

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Lung Cancer

Editorial Office

Dear Editor,

We are very pleased and honored that our manuscript has deserved attention for publication in **Lung Cancer**. Moreover, we thank you very much for the thoughtful and constructive review of our paper. Therefore, we carefully read the comments and suggestions made by Reviewer #1 and modified the manuscript accordingly. So, please find enclosed the *point-by-point* response.

While we hope that you will find the revised version of the manuscript acceptable for publication as an original article in your journal we will be happy to further respond to comments and queries, should they occur.

Best regards,

Roberto Tonelli, MD

Lung Cancer

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Comments from Reviewer 1

Reviewer 1

Reviewer #1: Retrospective cohort study with control arm comparing n=60 interventional bronchoscopy at outset of treatment (predominantly stenting, some debulking) in addition to chemoradiotherapy vs chemoradiotherapy alone n=40 in malignant central airways obstruction in Stage IIIb NSCLC. Clinically and statistically significant primary outcome of improved 12 month survival. A nice study with a strong hypothesis forming outcome which may lead to more meaningful practice changing multicentre/prospective/randomised work.

We really thank the Reviewer for the accurate reviewing process of our work. We are also grateful for the appreciation of our study. We have welcomed all of his/her comments and we have tried to amend the manuscript accordingly.

Reviewer 1's comment 1

(1) Did all patients undergo initial flexible bronchoscopic workup?

Response to Reviewer 1's comment 1

We thank the Reviewer for this observation that gave us the chance to better clarify each of the points risen.

a) Figure 1 and 2nd line of Results/Population suggests this data was derived from CT scan. This can both over and underestimate the degree of luminal narrowing: in your reference number 6 for instance 31% of CAO was missed on dedicated CT scan review. Blood, mucous and endobronchial debris can overestimate obstructive effect of tumour. Was any note made of imaging/bronchoscopic correlation? And whether airway obstruction was intrinsic/extrinsic/mixed?

We agree with the Reviewer that CT scan might under and/or overestimate the grade of CAO. All the patients enrolled had undergone flexible bronchoscopy whose reports were considered, alongside CT scan images, in order to estimate the extension of CAO. We have better specified this point in the methods section. Regarding the nature of the obstruction, we did not specify whether it was intrinsic/extrinsic/mixed given the paucity of data collected on this point due to the retrospective design of the study.

b) How was diagnosis and staging of NSCLC performed? Given all stage IIIb (N2 or N3 disease), presume most via EBUS TBNA however a needle biopsy of a supraclavicular node may sufficiently make a diagnosis. 'Population and measures' does state 'histologic diagnosis' however -> these are cytologic methods unless cores are obtained. Were all diagnoses made histologically?

We agree with the Reviewer that patients whose diagnosis was made via EBUS TBNA had a “cytologic” diagnosis and we have amended the manuscript accordingly. Given the long retrospective time frame (10 years) only a portion of patients was staged through EBUS TBNA. Thus, for all patients we have considered staging performed with PEC-CT scan assessment.

c) Timeframe between diagnosis, interventional bronchoscopy procedures and chemoradiotherapy?

We thank the Reviewer for this question. All patients enrolled were treated within a median time frame of 7 days (1-12) from diagnosis. Thereafter, they underwent sequential chemoradiotherapy within 5 (1-8) days from the endoscopic treatment.

d) Did any patients undergo debulking procedures via flexible bronchoscopy at time of diagnosis eg wire snare removal of polypoid endobronchial tumours?

We thank the Reviewer for this question. None of the patients underwent debulking via flexible bronchoscopy but all of them were treated through rigid bronchoscopy.

Reviewer 1’s comment 2

(2) There is no mention of patient symptomatology in each group - I understand the retrospective nature doesn't lend itself to comparative symptom or quality of life scores but you do have symptom free time as a secondary outcome.

Response to Reviewer 1’s comment 2

We thank the Reviewer for this important comment. We have resumed available evidence of symptoms in a supplementary Table (see Table S2, supplementary materials).

Reviewer 1's comment 3

(3) Materials and Methods/Design states that a stent was used 'whenever indicated.' Can you please elaborate on this indication? Your reference 24 SPOC trial would suggest that stent placement post debulking of intrinsic tumour should not be considered in oncologic treatment naive patients (obviously recent paper, your data spans 10 years)

Response to Reviewer 1's comment 3

We thank the Reviewer for this relevant comment that gave us the chance to better clarify the indication for stent positioning procedure at our center. Patients underwent stent positioning in case of mixed (intrinsic/extrinsic) CAO and if a significant (>50%) stenosis persisted after debulking. We have added this point in the Methods section of the revised version.

a) Malignant CAO requiring stenting may use silicone or metal (covered or uncovered) stents. A brief comment on why silicone stents preferred? The implications of this choice, especially repeat procedures? Is the need for repeat bronchoscopy for stent management included in the secondary outcome 'hospitalisations?'

We thank the Reviewer for this comment. The use of silicone stent was mainly motivated by center expertise in this material. Moreover, it allows a more extensive coverage of the lesion avoiding neoplastic infiltration within metal mesh. Furthermore, in our experience the ultimate nitinol covered metal stents are subjected to cover deterioration resulting in neoplastic infiltration. We included the need for repeated bronchoscopy in the outcome "hospitalisations".

b) Table 2 does address some of the above but - type of stent 'Y' and 'single' adds up to 58 (but stenting procedure n=54). Did some patients have dual stents placed? Are all complications at 1 year all stent complications and 10 individuals had differing permutations of these issues? The data in this table should be clearer.

We thank the Reviewer for this comment. A number of patients had dual stent placement in case of extremely extensive CAO. The Table refers to the complications of patients who had integrated treatment (debulking only, stent only, debulking + stent). Ten patients presented the permutation of the different kind of complication over time (e.g. 6 patients presented occlusion and further dislocation and subsequent removal of the stent; of them 5 patients presented post-obstructive pneumonia, 2 patient presented granulation and one of them underwent stent removal, 2 patients presented dislocation without occlusion and were further subjected to removal). We have added this clarification in the legend of Table 2.

Reviewer 1's comment 4

(4) Did any patients in the standard care group require interventional bronchoscopy techniques during their treatment course? Would expect some given the significant degree of obstruction at time of diagnosis, the high rates of respiratory failure and palliative treatments depicted in table 4.

Response to Reviewer 1's comment 4

We thank the Reviewer for this comment. None of the patient in the standard care group underwent interventional bronchoscopy during the treatment course.

Reviewer 1's comment 5

(5) KRAS mutation status and left main bronchus involvement are known poor prognostic features. These are first flagged in the statistical analysis and appropriate background provided in the discussion section. Should these at least be touched upon in the introduction?

Response to Reviewer 1's minor comment 5

We welcome and thank the Reviewer for this comment. We have added a brief sentence in the introduction section to tackle with this concept as follows: "….*although some anatomical features (i.e. left bronchus involvement) alongside specific mutational status may worsen outcomes*".

Reviewer 1's comment 6

(6) In your discussion you want to consider the real advantage in survival. I would be interested in subgroups of debulking/stenting/both, hypothesising that the act of debulking intrinsic disease (perhaps more so in the KRAS mutant patients) has a greater impact and augmentation of subsequent therapy than stenting alone. The numbers would likely be small however and is hypothesis forming at best. The intervention being investigated is one or both of two procedures, in patients who may have intrinsic/extrinsic or mixed central airway obstruction. There remains inherent inescapable heterogeneity. Non-surgically appropriate IIIa patients with CAO could well have been included (but more challenging data retrieval) and may provide a more meaningful future recommendation. It should be mentioned why only IIIb were included. Agree with comment regarding studies including stage IV disease having an additional confounder.

Response to Reviewer 1's minor comment 6

We thank the Reviewer for these important comments. We have then run a new analysis by treatment subgroups. Although the limited group numbers, we found that debulking alone was associated with higher incidence of respiratory failure and re-hospitalization. The associated treatment between debulking and stenting resulted as the more effective treatment although small numbers did not allow to get any statistical significance. We have added Table S3 in the supplementary materials and a specific section in the Results. This point deserves to be further investigated in larger cohorts.

Regarding the potential inclusion of patient with stage 3A we agree with the Reviewer that those patients could have benefit from interventional treatment. However, we decided to include only stage 3B in order to obtain a more reliable survival gain in the analysis. We have thus added this point in the discussion section.

Reviewer 1's comment 7

(7) Table 1 lists PDL-1 n(%). Is this tumour proportion score? This is a continuous rather than binary variable. What percentage cutoff for PDL-1 is being used here?

Response to Reviewer 1's comment 7

We thank the Reviewer for this comment. PDL-1 feature is referred to patients with a PDL-1 expression above 50%. This point has been better specified in the revised version.

Reviewer 1's comment 8

(8) How has 'extensive involvement' been defined? Table 1 would suggest the numbers are the same as carina involvement?

Response to Reviewer 1's comment 8

We thank the Reviewer for this comment. Extensive involvement was defined as the involvement of trachea, carina and at least one main bronchus. The Reviewer correctly pointed out that the number of patients with the involvement of carina is the same of patients with extensive involvement. This might mean that in our population there were no patients with carina involvement without a simultaneous involvement of trachea and main bronchi.

Reviewer 1's comment 9

(9) Table 1 Histotype 'others' - what does this include? Predominantly NOS?

Response to Reviewer 1's comment 9

We thank the Reviewer for this comment. The feature "Histotype others" includes predominantly NOS (n=10, 67%) alongside large cells carcinoma (n=5, 33%). This point has been better specified in the revised version.

Reviewer 1's comment 10

(10) I feel highlights should be written in past tense - this study showed that x IMPROVED y, that doesn't mean that x IMPROVES y. Try to avoid acronyms in highlights.

Response to Reviewer 1's comment 10

We thank the Reviewer for this comment. We have amended highlights as suggested.

Highlights

- In a cohort of patients with locally advanced Non-Small Cell Lung Cancer and associated Central Airways Obstruction interventional bronchoscopy as a part of an integrated treatment improved 1-year survival.
- Interventional bronchoscopy reduced new hospitalizations, increased symptom-free interval and prevented atelectasis.
- Genetic and anatomic phenotyping might identify patients who may gain life expectancy from the endoscopic intervention.

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Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE)

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Disclosure of funding: none.

Conflict of interest: *the authors have no conflict of interest, nor financial involvement with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript*

Abstract

Objectives

Despite new therapeutic perspectives, the presence of central airways occlusion (CAO) in patients with locally advanced non-small cell lung cancer (NSCLC) is associated with poor survival. There is no clear evidence on the clinical impact of interventional bronchoscopy as a part of an integrated treatment to cure these patients.

Materials and methods

This retrospective cohort study was conducted in two teaching hospitals over a 10 years period (January 2010-January 2020) comparing patients with NSCLC at stage IIIB and CAO at disease onset treated with chemotherapy/radiotherapy (standard therapy-ST) with those receiving interventional bronchoscopy plus ST (integrated treatment-IT). Primary outcome was 1-year survival. The onset of respiratory events, symptoms-free interval, hospitalization, need for palliation, and overall mortality served as secondary outcomes.

Results

A total of 100 patients were included, 60 in the IT and 40 in the ST group. Unadjusted Kaplan-Meier estimates showed greater effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003). IT showed a significantly higher survival gain over ST in those patients showing KRAS mutation (7.6 VS 0.8 months,<0.0001), a lumen occlusion >65% (6.6 VS 2.9 months,<0.001), and lacking the involvement of left bronchus (7 VS 2.3 months,<0.0001). Compared to ST, IT also showed a favorable difference in terms of new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01).

Conclusions

In patients with NSCLC stage IIIB and CAO, additional interventional bronchoscopy might impact on 1-year survival. Genetic and anatomic phenotyping might allow identifying those patients who may gain life expectancy from the endoscopic intervention.

Key words: *Non-small cell lung cancer, central airway obstruction, therapeutic bronchoscopy, mechanical debulking, airway stent, KRAS-mutant tumors.*

Abbreviations: *CAO = central airway obstruction, CT = chemotherapy, RT = radiation therapy, ST = standard therapy, IT integrated treatment, NSCLC = Non-Small Cell Lung Cancer, IQR = interquartile ranges; EGFR = epidermal growth factor receptor; BRAF = v-raf murine sarcoma viral oncogene*

homolog B1; KRAS = Kirsten rat sarcoma; ALK = Anaplastic lymphoma kinase; PDL1 = programmed death-ligand 1; CHT = chemotherapy; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

Introduction

Stage III locally advanced non-small cell lung cancer (NSCLC) is a heterogeneous condition affecting about one-third of the overall patients (1). Usually, therapeutic approach consists of a combination of local therapy (radiotherapy) with systemic platinum-based doublet chemotherapy. However, the prognosis remains poor, with only a limited improvement in survival achieved over the past 10 years. Recently, it has been shown that durvalumab significantly prolonged progression-free and overall survival, as compared with placebo, among patients with unresectable stage III NSCLC after concurrent chemoradiotherapy (2-3). Despite this new therapeutic perspective, a group of patients with locally advanced NSCLC already presents at diagnosis with an occlusion of the central airways which can result in worse life expectancy.

Malignant central airway obstruction (CAO) is defined as any malignant disease process that causes significant alteration of patency of the trachea, main bronchi, or bronchus intermedius (4). It is estimated that 20-30% of patients with lung cancer will develop CAO with the associated complications (dyspnoea, atelectasis, post-obstructive pneumonia), and 40% of tumor-related mortality can be attributed to locoregional progression of lung cancer (5). Furthermore, some studies show that in advanced lung cancer, CAO is associated with poor survival when adjusted for age, gender and stage of cancer (6). In particular, in unresectable NSCLC stage IIIB with CAO, locoregional control of neoplastic disease could have a significant impact on survival.

Short-course of palliative radiotherapy may achieve significant control of airway stenosis in 23-54% of patients within 24 days (7-8). Interventional bronchoscopy (mechanical debulking and thermal techniques or implementation with tracheal/bronchial prostheses) allows for immediate relieving of airway occlusion in 93% of cases, leading to a significant improvement in symptoms and quality of life in almost 50% of patients (9).

To date, there is currently no reliable evidence regarding the impact of interventional bronchoscopy on survival in locally advanced NSCLC (10). The main purpose of this study is therefore to evaluate the clinical impact of interventional bronchoscopy plus chemotherapy/radiotherapy (integrated treatment) compared with chemotherapy/radiotherapy alone (standard therapy) in the management of patients with stage IIIB NSCLC with CAO.

Materials and methods

Design

EVERMORE is a retrospective, multicenter observational cohort study carried out in two units of Emilia Romagna region (Italy): Diagnostic and Interventional Bronchoscopy Unit of the University Hospital of Modena, and Thoracic Endoscopy Unit of the Santa Maria Nuova Hospital of Reggio Emilia. The two units have different protocols routinely applied to treat CAO in locally advanced NSCLC. In center A endoscopic treatment is performed early when stenosis exceeds 50%, even in the absence of respiratory symptoms, while in center B the other endoscopic treatment is performed only in CAO with associated respiratory symptoms. All interventional procedures have been performed in the operating room with a Dumon rigid bronchoscope (Efer Medical, La Ciotat, Cedex, France) under general anesthesia. Neodymium-doped yttrium aluminium garnet (Nd-YAG) laser photoresection (KLS Martin, Diode-pumped Nd: YAG laser Limax ®, Germany) was performed at 15-30 watts and pulse duration of 0.5-1.0s. In cases with extrinsic compression from malignant occlusion, or whenever indicated, a silicone stent (NOVATECH Doumon stents, Boston Medical Products, Inc., Westborough, MA, USA) was placed.

Malignant CAO was defined as a luminal occlusion of $\geq$ 50% in the trachea, mainstem bronchi and/or bronchus intermedius, consistent with previous studies (9). Clinical staging was based on the 8th lung cancer TNM classification (11).

This study was approved by Local Ethics Committee (Prot. AOU 0013040/19 and 276/2019/OSS/AOUMO) and registered on clinicaltrial.gov (trial registration number: NCT03903315).

Population and measures

From January 2010 to January 2020 we collected clinical, endoscopic and radiological data of NSCLC patients with CAO admitted in the two units. Inclusion criteria were as follows: age >18 years, candidates for anticancer treatment with histologic diagnosis of NSCLC stage IIIB and CAO at onset of disease, performance status $\leq$ 2, CAO in between 50% and 80%. Patients were excluded if aged > 80, and/or with end-stage chronic obstructive pulmonary disease, interstitial lung disease, life-threatening stenosis requiring urgent endoscopy.

Chart review, health record, medical record, archival data analysis was performed at each center. The following data have been collected in an electronic database: demographic data, Charlson Index for comorbidity assessment, histopathology, genetic analysis of the tumor (EGFR and KRAS mutations, ALK translocations), PD-L1 expression, localization of CAO, degree of airway obstruction, the type of anticancer treatment (chemotherapy, radiotherapy, tyrosine kinase inhibitors,

immunotherapy), type of endoscopic treatment (stent, laser and mechanical debulking), complications of endoscopic treatment, onset of respiratory events (atelectasis, infections, respiratory failure, hemorrhage), 1-year and overall survival, hospitalization rate, need for palliative care, symptoms-free interval. Patients included were divided into two groups: 1) integrated treatment-IT (patients undergoing endoscopic treatment plus chemotherapy/radiotherapy); 2) standard treatment-ST (chemotherapy/radiotherapy alone).

Outcomes

The primary purpose was to evaluate the impact on 12-month survival in patients with stage IIIB NSCLC with CAO in the two groups.

The secondary aim was similarly to compare the onset of respiratory events, hospitalization, need for palliative care, symptoms-free interval and overall survival (see in the previous paragraph).

Statistical Analysis

Sample size calculation was performed assuming an estimated 1-year mortality rate of 45% for IIIB NSCLC patients receiving ST with an estimated reduction by 40% in those receiving IT (data derived from an exploration analysis in 15 patients). Assuming $\alpha = 0.05$, power 80% and an enrollment ratio of 1:1.5 (according to the overall number of patients referred at each center), a sample size of 100 patients was calculated to perform analysis on the primary outcome.

Baseline characteristics of the participants treated with IT and ST were compared. Continuous variables were expressed as median and interquartile ranges (IQR) and compared by Kruskal Wallis test. Categorical variables were expressed as numbers and percentages (%) and compared by $\chi 2$ test or Fisher's exact test across the integrated and the standard treatment groups.

The 1-year survival analysis was performed with participants' follow-up accrued from the date of diagnosis until death. Time to death by groups was compared using unweighted Kaplan-Meier curves and univariable and multivariable Cox regression analysis with baseline fixed covariates. The effect of treatment was shown by means of unadjusted and adjusted hazard ratio (HR) with 95%CI. Two key confounders were identified as carina involvement and extensive involvement, as the most likely causes of treatment group assignment and outcome risk. In order to test the hypothesis that the difference between treatment groups might vary according to mutational status, severity of CAO and unfavorable location of the stenosis, we formally included an interaction term in the Cox regression model. Results were then showed after categorizing the population in two strata using

alternatively categorical separation for dichotomous variables (KRAS mutational status and left bronchus involvement) and the overall median value for continuous variables (percentage of lumen occlusion). Overall survival gain has been assessed according to the abovementioned stratification through ANOVA. The impact of the two different treatments on pre-specified secondary outcomes was carried out through Fisher's exact test. A two-sided test of less than 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp.New York, NY, USA) and Graphpad prism version 8.0 (Graphpad Software, Inc. La Jolla, Ca, USA) unless otherwise indicated.

Results

Population

A total amount of 7243 patients diagnosed with NSCLC were referred to center A and B over the considered period. Out of them, 730 (10%) presented CAO > 50% at the CT scan at the time of diagnosis. Among the 188 eligible subjects, 100 patients with CAO and stage IIIB NSCLC were included in the study. Their median follow-up from diagnosis was 21 (IQR=9-36) months. Study flow-chart is shown in Figure 1.

Demographics, type and site of malignancies, degree of CAO, mutational state of cancer and oncological therapies are presented in Table 1. Forty patients who underwent cancer therapy alone, represented the ST group, whereas 60 patients of the IT group underwent endoscopic treatment plus standard chemotherapy/radiotherapy. The two groups did not show differences in terms of demographic characteristics, degree of stenosis, histology, mutational status of cancer and modality of standard treatment (Table 1). Patients in IT group showed an higher prevalence of extensive stenosis (25% VS 5%, p=0.01) and carina involvement (25% VS 5%, p=0.01) as compared to ST.

Overall, 90 patients received sequential chemo-radiotherapy with no difference between groups (p=0.5). Groups did not differ in the type of chemotherapy received (Table S1, supplementary materials). Types of recanalization techniques and complications related to endoscopic intervention as reported in the IT group are shown in Table 2.

Outcomes

Unadjusted Kaplan-Meier estimates showed the beneficial effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003) (Figure 2, panel A). After controlling for the key identified

confounders of carina and extensive involvement results were almost superimposable confirming the treatment difference observed in the unadjusted analysis (Table 3). Moreover, the stratified analyses showed that this difference varied by the degree of occlusion, the lack of main bronchus involvement, and the KRAS molecular status (Table 3) even after adjusting for the usual set of confounders. Kaplan-Meier curves also showed a significant survival benefit at 1-year for the abovementioned patients' strata when receiving IT as compared with ST (Figure A, panel B-D). Overall survival was longer in IT group although not statistically significant (23.7 months VS 19.2 months, p=0.2). IT group showed a significantly higher survival gain over ST when patients had KRAS mutation (7.6 months VS 0.8 months, <0.0001), a lumen occlusion > 65% (6.6 months VS 2.9 months, <0.001), and no involvement of left bronchus (7 months VS 2.3 months, <0.0001) (Figure 3).

Finally, IT showed a statistically significant favorable difference in terms of overall new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01), but not for occurrence of infections or hemorrhage (p=0.7 and p=0.8 respectively), onset of respiratory failure (p=0.1), use of palliative care (p=0.9) (Table 4).

Discussion

This study shows that the integration of interventional bronchoscopy (used outside palliation) with chemotherapy/radiotherapy in the management of IIIB NSCLC with CAO has a significant impact on the patient's prognosis. Moreover, the greater gain in life expectancy would be closely related to cancer's anatomical (airway occlusion> 65%, no left mainstem occlusion), and molecular (KRAS-mutant NSCLC) features.

The prognosis of stage IIIB lung cancer is poor, and local control as well as systemic treatment are essential. The standard of care in unresectable stage III disease is a combination of platinum-based chemotherapy with radiation therapy (1). In recent years, the introduction of target therapy and immune-checkpoint inhibitors opened up new perspectives of treatment. In particular, the synergic effect between immune therapy and radiotherapy has been recently proved, thus this combination has become a new standard in stage III patients (2,3,12).

A proportion of IIIB NSCLC has a central airway occlusion that can occur at onset or during the course of the disease (4-5). In these patients, loco-regional progression of the disease can be one of the main causes of cancer-related death. Therefore, timing and technique of local disease control could have a significant impact on survival. Interventional bronchoscopy allows for rapid recanalization of airway obstruction, and it can be useful in locoregional control, by integrating with chemo-radiant

treatment in patients with locally advanced NSCLC (10). Some studies show that the technical success rate of this treatment, defined as restoration of airway patency of at least 50% of the original airway diameter, approximates 90% in experienced centers (9, 13-14).

Although the role of interventional bronchoscopy in the palliation of symptoms is well recognized, no data are currently available on the prognostic impact when using this technique in association with chemo/radiotherapy in stage IIIB NSCLC. Retrospectively, we were able to show a clear 1-year survival advantage when local interventional bronchoscopy is combined with medical therapies in patients with CAO.

Although this result appears relevant, some considerations must be taken regarding the timing of intervention, the real impact of the technique on life expectancy, and the influence of cancer's molecular features.

First, the threshold of airway narrowing requiring interventional bronchoscopy is not standardized. Being considered palliative, endoscopic intervention is often performed when symptoms are present, and the degree of obstruction is very severe (10). Dyspnea in patients with CAO is not related to the alteration of gas exchange, but to the increased work of breathing required to maintain a normal flow of air delivered to and from the lung. Therefore, at least theoretically, pressure drop (ΔP) over the stenosis is the main parameter that can be considered as a cause of increased work of breathing and appearances of symptoms. In a computational fluid dynamics (CFD) study, flow patterns and ΔP over different degrees of tracheal stenosis artificially inserted into a three-dimensional upper airway model were assessed. ΔP over the stenosis was seen to increase dramatically only if >70% of tracheal lumen was occluded (15). Thus, bronchoscopy treatment in NSCLC is often proposed when the narrowing of the airways is extreme, and the risks of the intervention can be relevant. In our cohort, we therefore excluded patients with severe stenosis (>80%) and patients who required emergency intervention due to respiratory distress. Notwithstanding, present data suggest that interventional bronchoscopy over standard treatment, may have a potential impact on outcome when proposed early in the management of stage IIIB NSCLC with CAO.

Second, we should consider which is the real advantage in survival following interventional bronchoscopy in stage IIIB NSCLC. Previous studies have analyzed the outcome of NSCLC patients undergoing interventional bronchoscopy in an heterogeneous populations, mixing up locally advanced NSCLC and stage IV, without a reliable control group, providing inconclusive results (16-24). Some data suggest that there is no difference in survival between patients free from CAO

receiving chemotherapy, compared to those symptomatics who underwent successful interventional bronchoscopy followed by adjuvant chemotherapy (16). In our study, the different approach to endoscopic treatment of CAO (stenosis > 50%) allowed the enrollment of a reliable control group. In addition, only stage IIIB patients were considered for the study main purpose. Indeed, 1-year survival significantly improved in the IT group compared to ST, however, if we consider the gain in life expectancy, a substantial survival effect was found in specific subsets of patients. Obstruction > 65% of the airway lumen, and no left mainstem occlusion were two anatomical features associated with a significant gain in survival. While it may be intuitive that resolving airway obstruction > 65% can result in a survival advantage, the explanation regarding the involvement of the left mainstem on the prognosis is less self-evident. Several studies have evaluated the technical success rate of therapeutic bronchoscopy in CAO, raising up the issue of patient selection (9,25). In the multi-institutional ACCP Quality Improvement Registry Evaluation, and Education (AQuIRE) registry, left mainstem obstruction was an unfavorable factor for the technical success of interventional bronchoscopy (9). Therefore, this result in our study could be explained by the greater technical difficulty in performing rigid bronchoscopy in cases of CAO with distal involvement of the left main bronchus.

Third, molecular cancer features also had the greatest impact on gain in life expectancy. In our cohort, patients with KRAS-mutant NSCLC had 7.6 months gain in life expectancy in IT patients compared to ST. Although there is no a valid cut-off to define the survival gain as clinically relevant, some studies indicate a threshold greater than 4-5 months to consider a solid therapeutic progress (26-28). Moreover, considering that unresectable stage IIIB NSCLC is an aggressive disease with poor outcome, the gain in life expectancy found in the IT group is an impressive result. KRAS mutations are found in approximately 20-25% of lung adenocarcinomas in Western countries and in 10-15% of cases in Asia (29-31). The mutation occurs mainly at codon 12 (>80%) and 13, causing a constitutive activation of the RAS oncoprotein and its intracellular pathways, resulting in uncontrolled cell proliferation and abnormal cell survival (32). Considering that KRAS-mutant lung cancer has been generally associated with lower survival and lower sensitivity to chemotherapy or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, it is reasonable to assume that in this subset of patients standard chemotherapy/radiotherapy is unable to achieve the local control of occlusive disease.

Although present findings are intriguing, we cannot draw a definitive conclusion due to several limitations of the study. This is mainly because of the retrospective design and the limited sample

size, whose calculation might have been biased. Last, patients have been treated in centers with high expertise in interventional pulmonology, therefore the validity of data cannot be extrapolated for all. Notwithstanding, results are promising and suggest that, interventional bronchoscopy should be considered early as an integral part of management of patients with NSCLC stage IIIB and CAO.

Conclusions

In patients with NSCLC stage IIIB and associated CAO, interventional bronchoscopy does not target only a palliative purpose but might impact survival. Genetic and anatomic phenotyping might allow identifying those patients who are more likely to gain in life expectancy from endoscopic intervention. Further prospective investigations in larger cohorts is warranted to confirm results.

Acknowledgments

None.

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Figure legends

Fig. 1. Flow chart for patients in this study.

Fig. 2. Kaplan-Mayer curves showing impact of integrated treatment compared to standard therapy on 1-year survival for the overall population (panel A), for patients presenting K-RAS mutation (panel B), for patients with lumen occlusion > 65% (panel C) and for patients with lack of left bronchus involvement (panel D).

Fig. 3. Comparison of survival gain of integrated treatment over standard therapy for patients presenting K-RAS mutation (left side), for patients with lumen occlusion > 65% (central part) and for patients with lack of left bronchus involvement (right side).

Author contribution

AM and DA have made substantial contributions to conception of the study, therefore they should both be considered as first authors. NF, RP, AA, ST, EC, FF, GFC and EM reviewed the literature, wrote the manuscript and produced the figures. MD, MB, FB, FG and GB reviewed the literature and wrote the manuscript. RF, LC and IC designed the study, elaborate data and wrote the manuscript. RT designed the study, performed the analysis, wrote and reviewed the manuscript. EC reviewed and edited the manuscript. All authors have made substantial contributions to the conception, design and realization of the study.

Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE)

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Disclosure of funding: none.

Conflict of interest: *the authors have no conflict of interest, nor financial involvement with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript*

Abstract

Objectives

Despite new therapeutic perspectives, the presence of central airways occlusion (CAO) in patients with locally advanced non-small cell lung cancer (NSCLC) is associated with poor survival. There is no clear evidence on the clinical impact of interventional bronchoscopy as a part of an integrated treatment to cure these patients.

Materials and methods

This retrospective cohort study was conducted in two teaching hospitals over a 10 years period (January 2010-January 2020) comparing patients with NSCLC at stage IIIB and CAO at disease onset treated with chemotherapy/radiotherapy (standard therapy-ST) with those receiving interventional bronchoscopy plus ST (integrated treatment-IT). Primary outcome was 1-year survival. The onset of respiratory events, symptoms-free interval, hospitalization, need for palliation, and overall mortality served as secondary outcomes.

Results

A total of 100 patients were included, 60 in the IT and 40 in the ST group. Unadjusted Kaplan-Meier estimates showed greater effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003). IT showed a significantly higher survival gain over ST in those patients showing KRAS mutation (7.6 VS 0.8 months,<0.0001), a lumen occlusion >65% (6.6 VS 2.9 months,<0.001), and lacking the involvement of left bronchus (7 VS 2.3 months,<0.0001). Compared to ST, IT also showed a favorable difference in terms of new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01).

Conclusions

In patients with NSCLC stage IIIB and CAO, additional interventional bronchoscopy might impact on 1-year survival. Genetic and anatomic phenotyping might allow identifying those patients who may gain life expectancy from the endoscopic intervention.

Key words: *Non-small cell lung cancer, central airway obstruction, therapeutic bronchoscopy, mechanical debulking, airway stent, KRAS-mutant tumors.*

Abbreviations: *CAO = central airway obstruction, CT = chemotherapy, RT = radiation therapy, ST = standard therapy, IT integrated treatment, NSCLC = Non-Small Cell Lung Cancer, IQR = interquartile ranges; EGFR = epidermal growth factor receptor; BRAF = v-raf murine sarcoma viral oncogene*

homolog B1; KRAS = Kirsten rat sarcoma; ALK = Anaplastic lymphoma kinase; PDL1 = programmed death-ligand 1; CHT = chemotherapy; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

Introduction

Stage III locally advanced non-small cell lung cancer (NSCLC) is a heterogeneous condition affecting about one-third of the overall patients (1). Usually, therapeutic approach consists of a combination of local therapy (radiotherapy) with systemic platinum-based doublet chemotherapy. However, the prognosis remains poor, with only a limited improvement in survival achieved over the past 10 years. Recently, it has been shown that durvalumab significantly prolonged progression-free and overall survival, as compared with placebo, among patients with unresectable stage III NSCLC after concurrent chemoradiotherapy (2-3). Despite this new therapeutic perspective, a group of patients with locally advanced NSCLC already presents at diagnosis with an occlusion of the central airways which can result in worse life expectancy.

Malignant central airway obstruction (CAO) is defined as any malignant disease process that causes significant alteration of patency of the trachea, main bronchi, or bronchus intermedius (4). It is estimated that 20-30% of patients with lung cancer will develop CAO with the associated complications (dyspnoea, atelectasis, post-obstructive pneumonia), and 40% of tumor-related mortality can be attributed to locoregional progression of lung cancer (5). Furthermore, some studies show that in advanced lung cancer, CAO is associated with poor survival when adjusted for age, gender and stage of cancer (6). In particular, in unresectable NSCLC stage IIIB with CAO, locoregional control of neoplastic disease could have a significant impact on survival.

Short-course of palliative radiotherapy may achieve significant control of airway stenosis in 23-54% of patients within 24 days (7-8). Interventional bronchoscopy (mechanical debulking and thermal techniques or implementation with tracheal/bronchial prostheses) allows for immediate relieving of airway occlusion in 93% of cases, leading to a significant improvement in symptoms and quality of life in almost 50% of patients, although some anatomical features (i.e. left bronchus involvement) alongside specific mutational status may worsen outcomes. (9)

To date, there is currently no reliable evidence regarding the impact of interventional bronchoscopy on survival in locally advanced NSCLC (10). The main purpose of this study is therefore to evaluate the clinical impact of interventional bronchoscopy plus chemotherapy/radiotherapy (integrated treatment) compared with chemotherapy/radiotherapy alone (standard therapy) in the management of patients with stage IIIB NSCLC with CAO.

Materials and methods

Design

EVERMORE is a retrospective, multicenter observational cohort study carried out in two units of Emilia Romagna region (Italy): Diagnostic and Interventional Bronchoscopy Unit of the University Hospital of Modena, and Thoracic Endoscopy Unit of the Santa Maria Nuova Hospital of Reggio Emilia. The two units have different protocols routinely applied to treat CAO in locally advanced NSCLC. In center A endoscopic treatment is performed early when stenosis exceeds 50%, even in the absence of respiratory symptoms, while in center B the other endoscopic treatment is performed only in CAO with associated respiratory symptoms. In center A patients underwent stent positioning in case of mixed (intrinsic/extrinsic) CAO and if after debulking procedure a significant (>50%) stenosis persists. All interventional procedures have been performed in the operating room with a Dumon rigid bronchoscope (Efer Medical, La Ciotat, Cedex, France) under general anesthesia. Neodymium-doped yttrium aluminium garnet (Nd-YAG) laser photoresection (KLS Martin, Diode-pumped Nd: YAG laser Limax ®, Germany) was performed at 15-30 watts and pulse duration of 0.5-1.0s. In cases with extrinsic compression from malignant occlusion, or whenever indicated, a silicone stent (NOVATECH Doumon stents, Boston Medical Products, Inc., Westborough, MA, USA) was placed.

All patients had undergone flexible bronchoscopy whose reports were considered, alongside CT scan images, in order to estimate the extension of CAO. Malignant CAO was defined as a luminal occlusion of $\geq$ 50% in the trachea, mainstem bronchi and/or bronchus intermedius, consistent with previous studies (9). Clinical staging was based on the 8th lung cancer TNM classification (11).

This study was approved by Local Ethics Committee (Prot. AOU 0013040/19 and 276/2019/OSS/AOUMO) and registered on clinicaltrial.gov (trial registration number: NCT03903315).

Population and measures

From January 2010 to January 2020 we collected clinical, endoscopic and radiological data of NSCLC patients with CAO admitted in the two units. Inclusion criteria were as follows: age >18 years, candidates for anticancer treatment with cytologic and/or histologic diagnosis of NSCLC stage IIIB and CAO at onset of disease, performance status $\leq$ 2, CAO in between 50% and 80%. Patients were excluded if aged > 80, and/or with end-stage chronic obstructive pulmonary disease, interstitial lung disease, life-threatening stenosis requiring urgent endoscopy.

Chart review, health record, medical record, archival data analysis was performed at each center. The following data have been collected in an electronic database: demographic data, Charlson Index

for comorbidity assessment, histopathology, genetic analysis of the tumor (EGFR and KRAS mutations, ALK translocations), PD-L1 expression, localization of CAO, degree of airway obstruction, the type of anticancer treatment (chemotherapy, radiotherapy, tyrosine kinase inhibitors, immunotherapy), type of endoscopic treatment (stent, laser and mechanical debulking), complications of endoscopic treatment, onset of respiratory events (atelectasis, infections, respiratory failure, hemorrhage), 1-year and overall survival, hospitalization rate, need for palliative care, symptoms-free interval. Patients included were divided into two groups: 1) integrated treatment-IT (patients undergoing endoscopic treatment plus chemotherapy/radiotherapy); 2) standard treatment-ST (chemotherapy/radiotherapy alone).

Outcomes

The primary purpose was to evaluate the impact on 12-month survival in patients with stage IIIB NSCLC with CAO in the two groups.

The secondary aim was similarly to compare the onset of respiratory events, hospitalization, need for palliative care, symptoms-free interval and overall survival (see in the previous paragraph).

Statistical Analysis

Sample size calculation was performed assuming an estimated 1-year mortality rate of 45% for IIIB NSCLC patients receiving ST with an estimated reduction by 40% in those receiving IT (data derived from an exploration analysis in 15 patients). Assuming $\alpha = 0.05$, power 80% and an enrollment ratio of 1:1.5 (according to the overall number of patients referred at each center), a sample size of 100 patients was calculated to perform analysis on the primary outcome.

Baseline characteristics of the participants treated with IT and ST were compared. Continuous variables were expressed as median and interquartile ranges (IQR) and compared by Kruskal Wallis test. Categorical variables were expressed as numbers and percentages (%) and compared by $\chi 2$ test or Fisher's exact test across the integrated and the standard treatment groups.

The 1-year survival analysis was performed with participants' follow-up accrued from the date of diagnosis until death. Time to death by groups was compared using unweighted Kaplan-Meier curves and univariable and multivariable Cox regression analysis with baseline fixed covariates. The effect of treatment was shown by means of unadjusted and adjusted hazard ratio (HR) with 95%CI. Two key confounders were identified as carina involvement and extensive involvement, as the most likely causes of treatment group assignment and outcome risk. In order to test the hypothesis that

the difference between treatment groups might vary according to mutational status, severity of CAO and unfavorable location of the stenosis, we formally included an interaction term in the Cox regression model. Results were then showed after categorizing the population in two strata using alternatively categorical separation for dichotomous variables (KRAS mutational status and left bronchus involvement) and the overall median value for continuous variables (percentage of lumen occlusion). Overall survival gain has been assessed according to the abovementioned stratification through ANOVA. The impact of the two different treatments on pre-specified secondary outcomes was carried out through Fisher's exact test. Subgroup analysis according to interventional treatment procedure (debulking alone, stenting alone and both procedures) was also performed through Fisher's exact test. A two-sided test of less than 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp.New York, NY, USA) and Graphpad prism version 8.0 (Graphpad Software, Inc. La Jolla, Ca, USA) unless otherwise indicated.

Results

Population

A total amount of 7243 patients diagnosed with NSCLC were referred to center A and B over the considered period. Out of them, 730 (10%) presented CAO > 50% at the CT scan at the time of diagnosis. Among the 188 eligible subjects, 100 patients with CAO and stage IIIB NSCLC were included in the study. Their median follow-up from diagnosis was 21 (IQR=9-36) months. Study flow-chart is shown in Figure 1.

Demographics, type and site of malignancies, degree of CAO, mutational state of cancer and oncological therapies are presented in Table 1. Forty patients who underwent cancer therapy alone, represented the ST group, whereas 60 patients of the IT group underwent endoscopic treatment plus standard chemotherapy/radiotherapy. The two groups did not show differences in terms of demographic characteristics, degree of stenosis, histology, mutational status of cancer and modality of standard treatment (Table 1). Patients in IT group showed an higher prevalence of extensive stenosis (25% VS 5%, p=0.01) and carina involvement (25% VS 5%, p=0.01) as compared to ST.

Overall, 90 patients received sequential chemo-radiotherapy with no difference between groups (p=0.5). Groups did not differ in the type of chemotherapy received (Table S1, supplementary materials). Types of recanalization techniques and complications related to endoscopic intervention as reported in the IT group are shown in Table 2.

Outcomes

Unadjusted Kaplan-Meier estimates showed the beneficial effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003) (Figure 2, panel A). After controlling for the key identified confounders of carina and extensive involvement results were almost superimposable confirming the treatment difference observed in the unadjusted analysis (Table 3). Moreover, the stratified analyses showed that this difference varied by the degree of occlusion, the lack of main bronchus involvement, and the KRAS molecular status (Table 3) even after adjusting for the usual set of confounders. Kaplan-Meier curves also showed a significant survival benefit at 1-year for the abovementioned patients' strata when receiving IT as compared with ST (Figure A, panel B-D). Overall survival was longer in IT group although not statistically significant (23.7 months VS 19.2 months, p=0.2). IT group showed a significantly higher survival gain over ST when patients had KRAS mutation (7.6 months VS 0.8 months, <0.0001), a lumen occlusion > 65% (6.6 months VS 2.9 months, <0.001), and no involvement of left bronchus (7 months VS 2.3 months, <0.0001) (Figure 3).

Finally, IT showed a statistically significant favorable difference in terms of overall new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01), but not for occurrence of infections or hemorrhage (p=0.7 and p=0.8 respectively), onset of respiratory failure (p=0.1), use of palliative care (p=0.9) (Table 4). Subgroups analysis within interventional procedures showed that debulking alone was significantly associated with higher incidence of respiratory failure and re-hospitalization as compared to stenting alone or both the procedures (p=0.002 an p=0.001, Table 3, supplementary materials).

Discussion

This study shows that the integration of interventional bronchoscopy (used outside palliation) with chemotherapy/radiotherapy in the management of IIIB NSCLC with CAO has a significant impact on the patient's prognosis. Moreover, the greater gain in life expectancy would be closely related to cancer's anatomical (airway occlusion> 65%, no left mainstem occlusion), and molecular (KRAS-mutant NSCLC) features.

The prognosis of stage IIIB lung cancer is poor, and local control as well as systemic treatment are essential. The standard of care in unresectable stage III disease is a combination of platinum-based chemotherapy with radiation therapy (1). In recent years, the introduction of target therapy and immune-checkpoint inhibitors opened up new perspectives of treatment. In particular, the synergic

effect between immune therapy and radiotherapy has been recently proved, thus this combination has become a new standard in stage III patients (2,3,12).

A proportion of IIIB NSCLC has a central airway occlusion that can occur at onset or during the course of the disease (4-5). In these patients, loco-regional progression of the disease can be one of the main causes of cancer-related death. Therefore, timing and technique of local disease control could have a significant impact on survival. Interventional bronchoscopy allows for rapid recanalization of airway obstruction, and it can be useful in locoregional control, by integrating with chemo-radiant treatment in patients with locally advanced NSCLC (10). Some studies show that the technical success rate of this treatment, defined as restoration of airway patency of at least 50% of the original airway diameter, approximates 90% in experienced centers (9, 13-14).

Although the role of interventional bronchoscopy in the palliation of symptoms is well recognized, no data are currently available on the prognostic impact when using this technique in association with chemo/radiotherapy in stage IIIB NSCLC. Retrospectively, we were able to show a clear 1-year survival advantage when local interventional bronchoscopy is combined with medical therapies in patients with CAO.

Although this result appears relevant, some considerations must be taken regarding the timing of intervention, the real impact of the technique on life expectancy, and the influence of cancer's molecular features.

First, the threshold of airway narrowing requiring interventional bronchoscopy is not standardized. Being considered palliative, endoscopic intervention is often performed when symptoms are present, and the degree of obstruction is very severe (10). Dyspnea in patients with CAO is not related to the alteration of gas exchange, but to the increased work of breathing required to maintain a normal flow of air delivered to and from the lung. Therefore, at least theoretically, pressure drop (ΔP) over the stenosis is the main parameter that can be considered as a cause of increased work of breathing and appearances of symptoms. In a computational fluid dynamics (CFD) study, flow patterns and ΔP over different degrees of tracheal stenosis artificially inserted into a three-dimensional upper airway model were assessed. ΔP over the stenosis was seen to increase dramatically only if >70% of tracheal lumen was occluded (15). Thus, bronchoscopy treatment in NSCLC is often proposed when the narrowing of the airways is extreme, and the risks of the intervention can be relevant. In our cohort, we therefore excluded patients with severe stenosis (>80%) and patients who required emergency intervention due to respiratory distress. Notwithstanding, present data suggest that interventional bronchoscopy over standard treatment,

may have a potential impact on outcome when proposed early in the management of stage IIIB NSCLC with CAO.

Second, we should consider which is the real advantage in survival following interventional bronchoscopy in stage IIIB NSCLC. Previous studies have analyzed the outcome of NSCLC patients undergoing interventional bronchoscopy in a heterogeneous population, mixing up locally advanced NSCLC and stage IV, without a reliable control group, providing inconclusive results (16-24). Some data suggest that there is no difference in survival between patients free from CAO receiving chemotherapy, compared to those symptomatics who underwent successful interventional bronchoscopy followed by adjuvant chemotherapy (16). In our study, the different approach to endoscopic treatment of CAO (stenosis > 50%) allowed the enrollment of a reliable control group. In addition, only stage IIIB patients were considered for the study main purpose. It may be argued that non-surgically appropriate stage IIIA patients could benefit from interventional treatment. However, we decided to include only stage IIIB in the study in order to obtain a more reliable survival gain on the analysis performed. Indeed, 1-year survival significantly improved in the IT group compared to ST, however, if we consider the gain in life expectancy, a substantial survival effect was found in specific subsets of patients. Obstruction > 65% of the airway lumen, and no left mainstem occlusion were two anatomical features associated with a significant gain in survival. While it may be intuitive that resolving airway obstruction > 65% can result in a survival advantage, the explanation regarding the involvement of the left mainstem on the prognosis is less self-evident. Several studies have evaluated the technical success rate of therapeutic bronchoscopy in CAO, raising up the issue of patient selection (9,25). In the multi-institutional ACCP Quality Improvement Registry Evaluation, and Education (AQuIRE) registry, left mainstem obstruction was an unfavorable factor for the technical success of interventional bronchoscopy (9). Therefore, this result in our study could be explained by the greater technical difficulty in performing rigid bronchoscopy in cases of CAO with distal involvement of the left main bronchus.

Third, molecular cancer features also had the greatest impact on gain in life expectancy. In our cohort, patients with KRAS-mutant NSCLC had 7.6 months gain in life expectancy in IT patients compared to ST. Although there is no a valid cut-off to define the survival gain as clinically relevant, some studies indicate a threshold greater than 4-5 months to consider a solid therapeutic progress (26-28). Moreover, considering that unresectable stage IIIB NSCLC is an aggressive disease with poor outcome, the gain in life expectancy found in the IT group is an impressive result. KRAS mutations are found in approximately 20-25% of lung adenocarcinomas in Western countries and in 10-15%

of cases in Asia (29-31). The mutation occurs mainly at codon 12 (>80%) and 13, causing a constitutive activation of the RAS oncoprotein and its intracellular pathways, resulting in uncontrolled cell proliferation and abnormal cell survival (32). Considering that KRAS-mutant lung cancer has been generally associated with lower survival and lower sensitivity to chemotherapy or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, it is reasonable to assume that in this subset of patients standard chemotherapy/radiotherapy is unable to achieve the local control of occlusive disease.

Although present findings are intriguing, we cannot draw a definitive conclusion due to several limitations of the study. This is mainly because of the retrospective design and the limited sample size, whose calculation might have been biased. Last, patients have been treated in centers with high expertise in interventional pulmonology, therefore the validity of data cannot be extrapolated for all. Notwithstanding, results are promising and suggest that, interventional bronchoscopy should be considered early as an integral part of management of patients with NSCLC stage IIIB and CAO.

Conclusions

In patients with NSCLC stage IIIB and associated CAO, interventional bronchoscopy does not target only a palliative purpose but might impact survival. Genetic and anatomic phenotyping might allow identifying those patients who are more likely to gain in life expectancy from endoscopic intervention. Further prospective investigations in larger cohorts is warranted to confirm results.

Acknowledgments

None.

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Figure legends

Fig. 1. Flow chart for patients in this study.

Fig. 2. Kaplan-Mayer curves showing impact of integrated treatment compared to standard therapy on 1-year survival for the overall population (panel A), for patients presenting K-RAS mutation (panel B), for patients with lumen occlusion > 65% (panel C) and for patients with lack of left bronchus

involvement (panel D).

Fig. 3. Comparison of survival gain of integrated treatment over standard therapy for patients presenting K-RAS mutation (left side), for patients with lumen occlusion > 65% (central part) and for patients with lack of left bronchus involvement (right side).

Author contribution

AM and DA have made substantial contributions to conception of the study, therefore they should both be considered as first authors. NF, RP, AA, ST, EC, FF, GFC and EM reviewed the literature, wrote the manuscript and produced the figures. MD, MB, FB, FG and GB reviewed the literature and wrote the manuscript. RF, LC and IC designed the study, elaborate data and wrote the manuscript. RT designed the study, performed the analysis, wrote and reviewed the manuscript. EC reviewed and edited the manuscript. All authors have made substantial contributions to the conception, design and realization of the study.

Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE)

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Disclosure of funding: none.

Conflict of interest: *the authors have no conflict of interest, nor financial involvement with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript*

Abstract

Objectives

Despite new therapeutic perspectives, the presence of central airways occlusion (CAO) in patients with locally advanced non-small cell lung cancer (NSCLC) is associated with poor survival. There is no clear evidence on the clinical impact of interventional bronchoscopy as a part of an integrated treatment to cure these patients.

Materials and methods

This retrospective cohort study was conducted in two teaching hospitals over a 10 years period (January 2010-January 2020) comparing patients with NSCLC at stage IIIB and CAO at disease onset treated with chemotherapy/radiotherapy (standard therapy-ST) with those receiving interventional bronchoscopy plus ST (integrated treatment-IT). Primary outcome was 1-year survival. The onset of respiratory events, symptoms-free interval, hospitalization, need for palliation, and overall mortality served as secondary outcomes.

Results

A total of 100 patients were included, 60 in the IT and 40 in the ST group. Unadjusted Kaplan-Meier estimates showed greater effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003). IT showed a significantly higher survival gain over ST in those patients showing KRAS mutation (7.6 VS 0.8 months,<0.0001), a lumen occlusion >65% (6.6 VS 2.9 months,<0.001), and lacking the involvement of left bronchus (7 VS 2.3 months,<0.0001). Compared to ST, IT also showed a favorable difference in terms of new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01).

Conclusions

In patients with NSCLC stage IIIB and CAO, additional interventional bronchoscopy might impact on 1-year survival. Genetic and anatomic phenotyping might allow identifying those patients who may gain life expectancy from the endoscopic intervention.

Key words: *Non-small cell lung cancer, central airway obstruction, therapeutic bronchoscopy, mechanical debulking, airway stent, KRAS-mutant tumors.*

Abbreviations: *CAO = central airway obstruction, CT = chemotherapy, RT = radiation therapy, ST = standard therapy, IT integrated treatment, NSCLC = Non-Small Cell Lung Cancer, IQR = interquartile ranges; EGFR = epidermal growth factor receptor; BRAF = v-raf murine sarcoma viral oncogene*

homolog B1; KRAS = Kirsten rat sarcoma; ALK = Anaplastic lymphoma kinase; PDL1 = programmed death-ligand 1; CHT = chemotherapy; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

Introduction

Stage III locally advanced non-small cell lung cancer (NSCLC) is a heterogeneous condition affecting about one-third of the overall patients (1). Usually, therapeutic approach consists of a combination of local therapy (radiotherapy) with systemic platinum-based doublet chemotherapy. However, the prognosis remains poor, with only a limited improvement in survival achieved over the past 10 years. Recently, it has been shown that durvalumab significantly prolonged progression-free and overall survival, as compared with placebo, among patients with unresectable stage III NSCLC after concurrent chemoradiotherapy (2-3). Despite this new therapeutic perspective, a group of patients with locally advanced NSCLC already presents at diagnosis with an occlusion of the central airways which can result in worse life expectancy.

Malignant central airway obstruction (CAO) is defined as any malignant disease process that causes significant alteration of patency of the trachea, main bronchi, or bronchus intermedius (4). It is estimated that 20-30% of patients with lung cancer will develop CAO with the associated complications (dyspnoea, atelectasis, post-obstructive pneumonia), and 40% of tumor-related mortality can be attributed to locoregional progression of lung cancer (5). Furthermore, some studies show that in advanced lung cancer, CAO is associated with poor survival when adjusted for age, gender and stage of cancer (6). In particular, in unresectable NSCLC stage IIIB with CAO, locoregional control of neoplastic disease could have a significant impact on survival.

Short-course of palliative radiotherapy may achieve significant control of airway stenosis in 23-54% of patients within 24 days (7-8). Interventional bronchoscopy (mechanical debulking and thermal techniques or implementation with tracheal/bronchial prostheses) allows for immediate relieving of airway occlusion in 93% of cases, leading to a significant improvement in symptoms and quality of life in almost 50% of patients, although some anatomical features (i.e. left bronchus involvement) alongside specific mutational status may worsen outcomes. (9).

To date, there is currently no reliable evidence regarding the impact of interventional bronchoscopy on survival in locally advanced NSCLC (10). The main purpose of this study is therefore to evaluate the clinical impact of interventional bronchoscopy plus chemotherapy/radiotherapy (integrated treatment) compared with chemotherapy/radiotherapy alone (standard therapy) in the management of patients with stage IIIB NSCLC with CAO.

Materials and methods

Design

EVERMORE is a retrospective, multicenter observational cohort study carried out in two units of Emilia Romagna region (Italy): Diagnostic and Interventional Bronchoscopy Unit of the University Hospital of Modena, and Thoracic Endoscopy Unit of the Santa Maria Nuova Hospital of Reggio Emilia. The two units have different protocols routinely applied to treat CAO in locally advanced NSCLC. In center A endoscopic treatment is performed early when stenosis exceeds 50%, even in the absence of respiratory symptoms, while in center B the other endoscopic treatment is performed only in CAO with associated respiratory symptoms. In center A patients underwent stent positioning in case of mixed (intrinsic/extrinsic) CAO and if after debulking procedure a significant (>50%) stenosis persists. All interventional procedures have been performed in the operating room with a Dumon rigid bronchoscope (Efer Medical, La Ciotat, Cedex, France) under general anesthesia. Neodymium-doped yttrium aluminium garnet (Nd-YAG) laser photoresection (KLS Martin, Diode-pumped Nd: YAG laser Limax ®, Germany) was performed at 15-30 watts and pulse duration of 0.5-1.0s. In cases with extrinsic compression from malignant occlusion, or whenever indicated, a silicone stent (NOVATECH Doumon stents, Boston Medical Products, Inc., Westborough, MA, USA) was placed.

All patients had undergone flexible bronchoscopy whose reports were considered, alongside CT scan images, in order to estimate the extension of CAO. Malignant CAO was defined as a luminal occlusion of ≥ 50% in the trachea, mainstem bronchi and/or bronchus intermedius, consistent with previous studies (9). Clinical staging was based on the 8th lung cancer TNM classification (11).

This study was approved by Local Ethics Committee (Prot. AOU 0013040/19 and 276/2019/OSS/AOUMO) and registered on clinicaltrial.gov (trial registration number: NCT03903315).

Population and measures

From January 2010 to January 2020 we collected clinical, endoscopic and radiological data of NSCLC patients with CAO admitted in the two units. Inclusion criteria were as follows: age >18 years, candidates for anticancer treatment with cytologic and/or histologic diagnosis of NSCLC stage IIIB and CAO at onset of disease, performance status ≤ 2, CAO in between 50% and 80%. Patients were excluded if aged > 80, and/or with end-stage chronic obstructive pulmonary disease, interstitial lung disease, life-threatening stenosis requiring urgent endoscopy.

Chart review, health record, medical record, archival data analysis was performed at each center. The following data have been collected in an electronic database: demographic data, Charlson Index

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for comorbidity assessment, histopathology, genetic analysis of the tumor (EGFR and KRAS mutations, ALK translocations), PD-L1 expression, localization of CAO, degree of airway obstruction, the type of anticancer treatment (chemotherapy, radiotherapy, tyrosine kinase inhibitors, immunotherapy), type of endoscopic treatment (stent, laser and mechanical debulking), complications of endoscopic treatment, onset of respiratory events (atelectasis, infections, respiratory failure, hemorrhage), 1-year and overall survival, hospitalization rate, need for palliative care, symptoms-free interval. Patients included were divided into two groups: 1) integrated treatment-IT (patients undergoing endoscopic treatment plus chemotherapy/radiotherapy); 2) standard treatment-ST (chemotherapy/radiotherapy alone).

Outcomes

The primary purpose was to evaluate the impact on 12-month survival in patients with stage IIIB NSCLC with CAO in the two groups.

The secondary aim was similarly to compare the onset of respiratory events, hospitalization, need for palliative care, symptoms-free interval and overall survival (see in the previous paragraph).

Statistical Analysis

Sample size calculation was performed assuming an estimated 1-year mortality rate of 45% for IIIB NSCLC patients receiving ST with an estimated reduction by 40% in those receiving IT (data derived from an exploration analysis in 15 patients). Assuming $\alpha = 0.05$, power 80% and an enrollment ratio of 1:1.5 (according to the overall number of patients referred at each center), a sample size of 100 patients was calculated to perform analysis on the primary outcome.

Baseline characteristics of the participants treated with IT and ST were compared. Continuous variables were expressed as median and interquartile ranges (IQR) and compared by Kruskal Wallis test. Categorical variables were expressed as numbers and percentages (%) and compared by $\chi 2$ test or Fisher's exact test across the integrated and the standard treatment groups.

The 1-year survival analysis was performed with participants' follow-up accrued from the date of diagnosis until death. Time to death by groups was compared using unweighted Kaplan-Meier curves and univariable and multivariable Cox regression analysis with baseline fixed covariates. The effect of treatment was shown by means of unadjusted and adjusted hazard ratio (HR) with 95%CI. Two key confounders were identified as carina involvement and extensive involvement, as the most likely causes of treatment group assignment and outcome risk. In order to test the hypothesis that

the difference between treatment groups might vary according to mutational status, severity of CAO and unfavorable location of the stenosis, we formally included an interaction term in the Cox regression model. Results were then showed after categorizing the population in two strata using alternatively categorical separation for dichotomous variables (KRAS mutational status and left bronchus involvement) and the overall median value for continuous variables (percentage of lumen occlusion). Overall survival gain has been assessed according to the abovementioned stratification through ANOVA. The impact of the two different treatments on pre-specified secondary outcomes was carried out through Fisher's exact test. Subgroup analysis according to interventional treatment procedure (debulking alone, stenting alone and both procedures) was also performed through Fisher's exact test. A two-sided test of less than 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp.New York, NY, USA) and Graphpad prism version 8.0 (Graphpad Software, Inc. La Jolla, Ca, USA) unless otherwise indicated.

Results

Population

A total amount of 7243 patients diagnosed with NSCLC were referred to center A and B over the considered period. Out of them, 730 (10%) presented CAO > 50% at the CT scan at the time of diagnosis. Among the 188 eligible subjects, 100 patients with CAO and stage IIIB NSCLC were included in the study. Their median follow-up from diagnosis was 21 (IQR=9-36) months. Study flow-chart is shown in Figure 1.

Demographics, type and site of malignancies, degree of CAO, mutational state of cancer and oncological therapies are presented in Table 1. Forty patients who underwent cancer therapy alone, represented the ST group, whereas 60 patients of the IT group underwent endoscopic treatment plus standard chemotherapy/radiotherapy. The two groups did not show differences in terms of demographic characteristics, degree of stenosis, histology, mutational status of cancer and modality of standard treatment (Table 1). Patients in IT group showed an higher prevalence of extensive stenosis (25% VS 5%, p=0.01) and carina involvement (25% VS 5%, p=0.01) as compared to ST.

Overall, 90 patients received sequential chemo-radiotherapy with no difference between groups (p=0.5). Groups did not differ in the type of chemotherapy received (Table S1, supplementary materials). Types of recanalization techniques and complications related to endoscopic intervention as reported in the IT group are shown in Table 2.

Outcomes

Unadjusted Kaplan-Meier estimates showed the beneficial effect of IT compared to ST on 1-year survival (HR=2.1 95%CI[1.1-4.8], p=0.003) (Figure 2, panel A). After controlling for the key identified confounders of carina and extensive involvement results were almost superimposable confirming the treatment difference observed in the unadjusted analysis (Table 3). Moreover, the stratified analyses showed that this difference varied by the degree of occlusion, the lack of main bronchus involvement, and the KRAS molecular status (Table 3) even after adjusting for the usual set of confounders. Kaplan-Meier curves also showed a significant survival benefit at 1-year for the abovementioned patients' strata when receiving IT as compared with ST (Figure A, panel B-D). Overall survival was longer in IT group although not statistically significant (23.7 months VS 19.2 months, p=0.2). IT group showed a significantly higher survival gain over ST when patients had KRAS mutation (7.6 months VS 0.8 months, <0.0001), a lumen occlusion > 65% (6.6 months VS 2.9 months, <0.001), and no involvement of left bronchus (7 months VS 2.3 months, <0.0001) (Figure 3).

Finally, IT showed a statistically significant favorable difference in terms of overall new hospitalizations (p=0.03), symptom-free interval (p=0.02), and onset of atelectasis (p=0.01), but not for occurrence of infections or hemorrhage (p=0.7 and p=0.8 respectively), onset of respiratory failure (p=0.1), use of palliative care (p=0.9) (Table 4). Subgroups analysis within interventional procedures showed that debulking alone was significantly associated with higher incidence of respiratory failure and re-hospitalization as compared to stenting alone ~~and~~or both the procedures (p=0.002 an p=0.001, Table 3, supplementary materials).

Discussion

This study shows that the integration of interventional bronchoscopy (used outside palliation) with chemotherapy/radiotherapy in the management of IIIB NSCLC with CAO has a significant impact on the patient's prognosis. Moreover, the greater gain in life expectancy would be closely related to cancer's anatomical (airway occlusion> 65%, no left mainstem occlusion), and molecular (KRAS-mutant NSCLC) features.

The prognosis of stage IIIB lung cancer is poor, and local control as well as systemic treatment are essential. The standard of care in unresectable stage III disease is a combination of platinum-based chemotherapy with radiation therapy (1). In recent years, the introduction of target therapy and immune-checkpoint inhibitors opened up new perspectives of treatment. In particular, the synergic

effect between immune therapy and radiotherapy has been recently proved, thus this combination has become a new standard in stage III patients (2,3,12).

A proportion of IIIB NSCLC has a central airway occlusion that can occur at onset or during the course of the disease (4-5). In these patients, loco-regional progression of the disease can be one of the main causes of cancer-related death. Therefore, timing and technique of local disease control could have a significant impact on survival. Interventional bronchoscopy allows for rapid recanalization of airway obstruction, and it can be useful in locoregional control, by integrating with chemo-radiant treatment in patients with locally advanced NSCLC (10). Some studies show that the technical success rate of this treatment, defined as restoration of airway patency of at least 50% of the original airway diameter, approximates 90% in experienced centers (9, 13-14).

Although the role of interventional bronchoscopy in the palliation of symptoms is well recognized, no data are currently available on the prognostic impact when using this technique in association with chemo/radiotherapy in stage IIIB NSCLC. Retrospectively, we were able to show a clear 1-year survival advantage when local interventional bronchoscopy is combined with medical therapies in patients with CAO.

Although this result appears relevant, some considerations must be taken regarding the timing of intervention, the real impact of the technique on life expectancy, and the influence of cancer's molecular features.

First, the threshold of airway narrowing requiring interventional bronchoscopy is not standardized. Being considered palliative, endoscopic intervention is often performed when symptoms are present, and the degree of obstruction is very severe (10). Dyspnea in patients with CAO is not related to the alteration of gas exchange, but to the increased work of breathing required to maintain a normal flow of air delivered to and from the lung. Therefore, at least theoretically, pressure drop (ΔP) over the stenosis is the main parameter that can be considered as a cause of increased work of breathing and appearances of symptoms. In a computational fluid dynamics (CFD) study, flow patterns and ΔP over different degrees of tracheal stenosis artificially inserted into a three-dimensional upper airway model were assessed. ΔP over the stenosis was seen to increase dramatically only if >70% of tracheal lumen was occluded (15). Thus, bronchoscopy treatment in NSCLC is often proposed when the narrowing of the airways is extreme, and the risks of the intervention can be relevant. In our cohort, we therefore excluded patients with severe stenosis (>80%) and patients who required emergency intervention due to respiratory distress. Notwithstanding, present data suggest that interventional bronchoscopy over standard treatment,

may have a potential impact on outcome when proposed early in the management of stage IIIB NSCLC with CAO.

Second, we should consider which is the real advantage in survival following interventional bronchoscopy in stage IIIB NSCLC. Previous studies have analyzed the outcome of NSCLC patients undergoing interventional bronchoscopy in ~~a~~an heterogeneous populations, mixing up locally advanced NSCLC and stage IV, without a reliable control group, providing inconclusive results (16-24). Some data suggest that there is no difference in survival between patients free from CAO receiving chemotherapy, compared to those symptomatics who underwent successful interventional bronchoscopy followed by adjuvant chemotherapy (16). In our study, the different approach to endoscopic treatment of CAO (stenosis > 50%) allowed the enrollment of a reliable control group. In addition, only stage IIIB patients were considered for the study main purpose. It may be argued that non-surgically appropriate stage IIIA patients could benefit from interventional treatment. However, we decided to include only stage IIIB in the study in order to obtain a more reliable ~~analysis on~~ survival gain on the analysis performed. Indeed, 1-year survival significantly improved in the IT group compared to ST, however, if we consider the gain in life expectancy, a substantial survival effect was found in specific subsets of patients. Obstruction > 65% of the airway lumen, and no left mainstem occlusion were two anatomical features associated with a significant gain in survival. While it may be intuitive that resolving airway obstruction > 65% can result in a survival advantage, the explanation regarding the involvement of the left mainstem on the prognosis is less self-evident. Several studies have evaluated the technical success rate of therapeutic bronchoscopy in CAO, raising up the issue of patient selection (9,25). In the multi-institutional ACCP Quality Improvement Registry Evaluation, and Education (AQuIRE) registry, left mainstem obstruction was an unfavorable factor for the technical success of interventional bronchoscopy (9). Therefore, this result in our study could be explained by the greater technical difficulty in performing rigid bronchoscopy in cases of CAO with distal involvement of the left main bronchus.

Third, molecular cancer features also had the greatest impact on gain in life expectancy. In our cohort, patients with KRAS-mutant NSCLC had 7.6 months gain in life expectancy in IT patients compared to ST. Although there is no a valid cut-off to define the survival gain as clinically relevant, some studies indicate a threshold greater than 4-5 months to consider a solid therapeutic progress (26-28). Moreover, considering that unresectable stage IIIB NSCLC is an aggressive disease with poor outcome, the gain in life expectancy found in the IT group is an impressive result. KRAS mutations

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are found in approximately 20-25% of lung adenocarcinomas in Western countries and in 10-15% of cases in Asia (29-31). The mutation occurs mainly at codon 12 (>80%) and 13, causing a constitutive activation of the RAS oncoprotein and its intracellular pathways, resulting in uncontrolled cell proliferation and abnormal cell survival (32). Considering that KRAS-mutant lung cancer has been generally associated with lower survival and lower sensitivity to chemotherapy or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, it is reasonable to assume that in this subset of patients standard chemotherapy/radiotherapy is unable to achieve the local control of occlusive disease.

Although present findings are intriguing, we cannot draw a definitive conclusion due to several limitations of the study. This is mainly because of the retrospective design and the limited sample size, whose calculation might have been biased. Last, patients have been treated in centers with high expertise in interventional pulmonology, therefore the validity of data cannot be extrapolated for all. Notwithstanding, results are promising and suggest that, interventional bronchoscopy should be considered early as an integral part of management of patients with NSCLC stage IIIB and CAO.

Conclusions

In patients with NSCLC stage IIIB and associated CAO, interventional bronchoscopy does not target only a palliative purpose but might impact survival. Genetic and anatomic phenotyping might allow identifying those patients who are more likely to gain in life expectancy from endoscopic intervention. Further prospective investigations in larger cohorts is warranted to confirm results.

Acknowledgments

None.

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Figure legends

Fig. 1. Flow chart for patients in this study.

Fig. 2. Kaplan-Mayer curves showing impact of integrated treatment compared to standard therapy on 1-year survival for the overall population (panel A), for patients presenting K-RAS mutation (panel B), for patients with lumen occlusion > 65% (panel C) and for patients with lack of left bronchus

involvement (panel D).

Fig. 3. Comparison of survival gain of integrated treatment over standard therapy for patients presenting K-RAS mutation (left side), for patients with lumen occlusion > 65% (central part) and for patients with lack of left bronchus involvement (right side).

Author contribution

AM and DA have made substantial contributions to conception of the study, therefore they should both be considered as first authors. NF, RP, AA, ST, EC, FF, GFC and EM reviewed the literature, wrote the manuscript and produced the figures. MD, MB, FB, FG and GB reviewed the literature and wrote the manuscript. RF, LC and IC designed the study, elaborate data and wrote the manuscript. RT designed the study, performed the analysis, wrote and reviewed the manuscript. EC reviewed and edited the manuscript. All authors have made substantial contributions to the conception, design and realization of the study.

Summary Conflict of interest Statement

Declarations of interest: none.

Roberto Tonelli, MD on behalf of all authors.

Figure 3

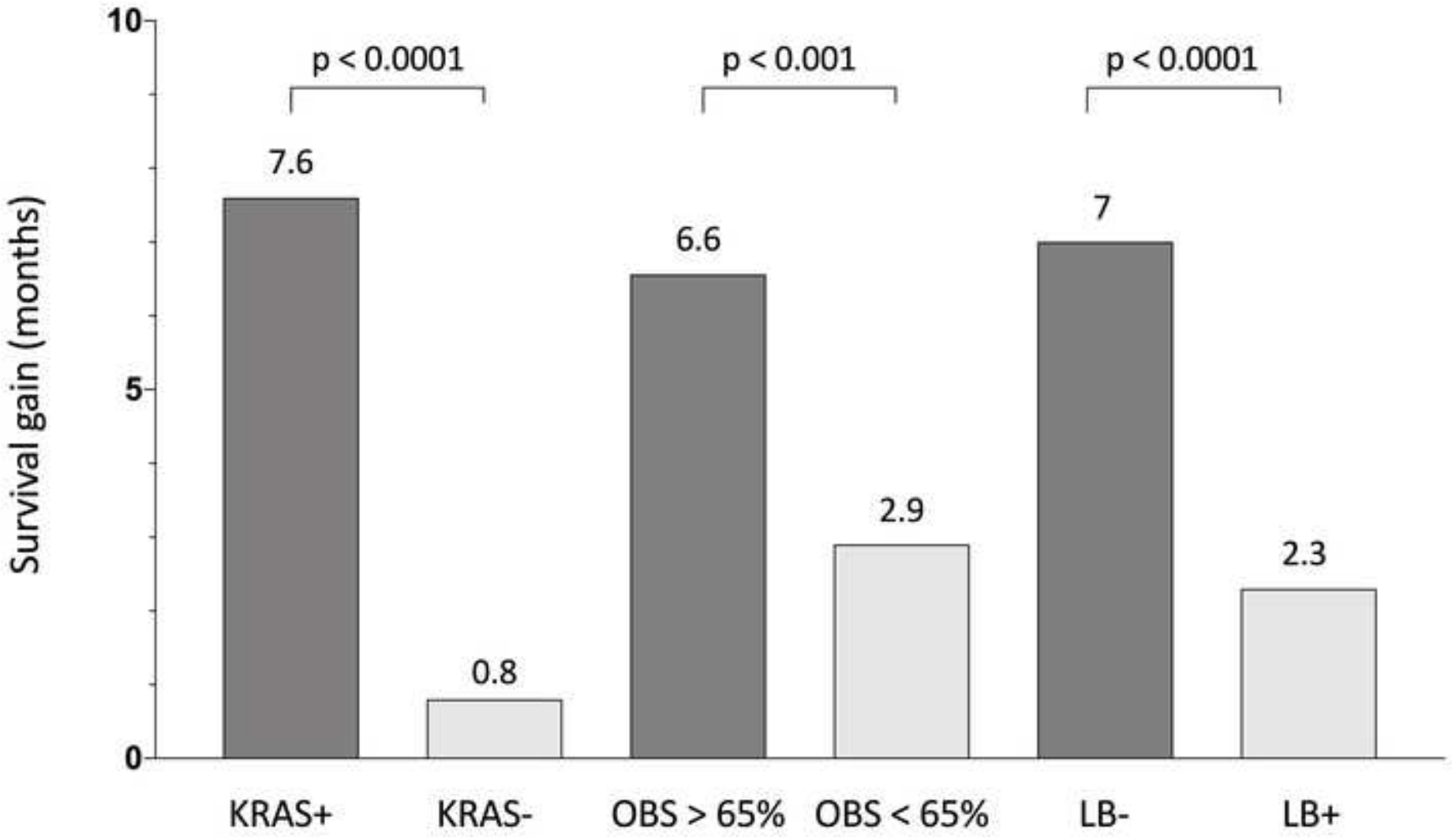
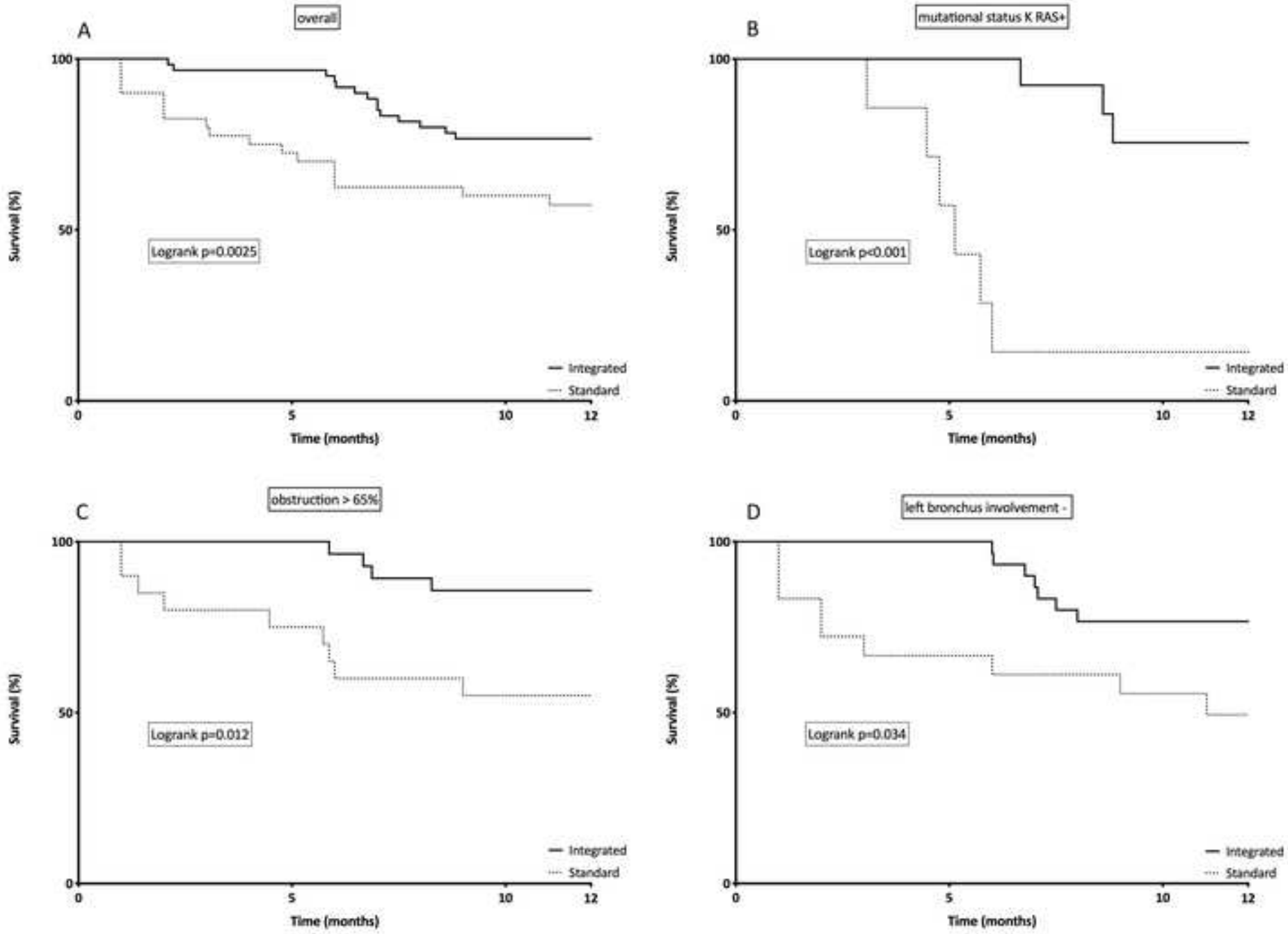

10
5
0
Survival gain (months)
p < 0.0001
p < 0.001
p < 0.0001
7.6
0.8
6.6
2.9
7
2.3
KRAS+
KRAS-
OBS > 65%
OBS < 65%
LB-
LB+

Figure 2


A
overall
Survival (%)
100
50
0
Logrank p=0.0025
Integrated
Standard
0
5
10
12
Time (months)
B
mutational status K RAS+
Survival (%)
100
50
0
Logrank p<0.001
Integrated
Standard
0
5
10
12
Time (months)
C
obstruction > 65%
Survival (%)
100
50
0
Logrank p=0.012
Integrated
Standard
0
5
10
12
Time (months)
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left bronchus involvement -
Survival (%)
100
50
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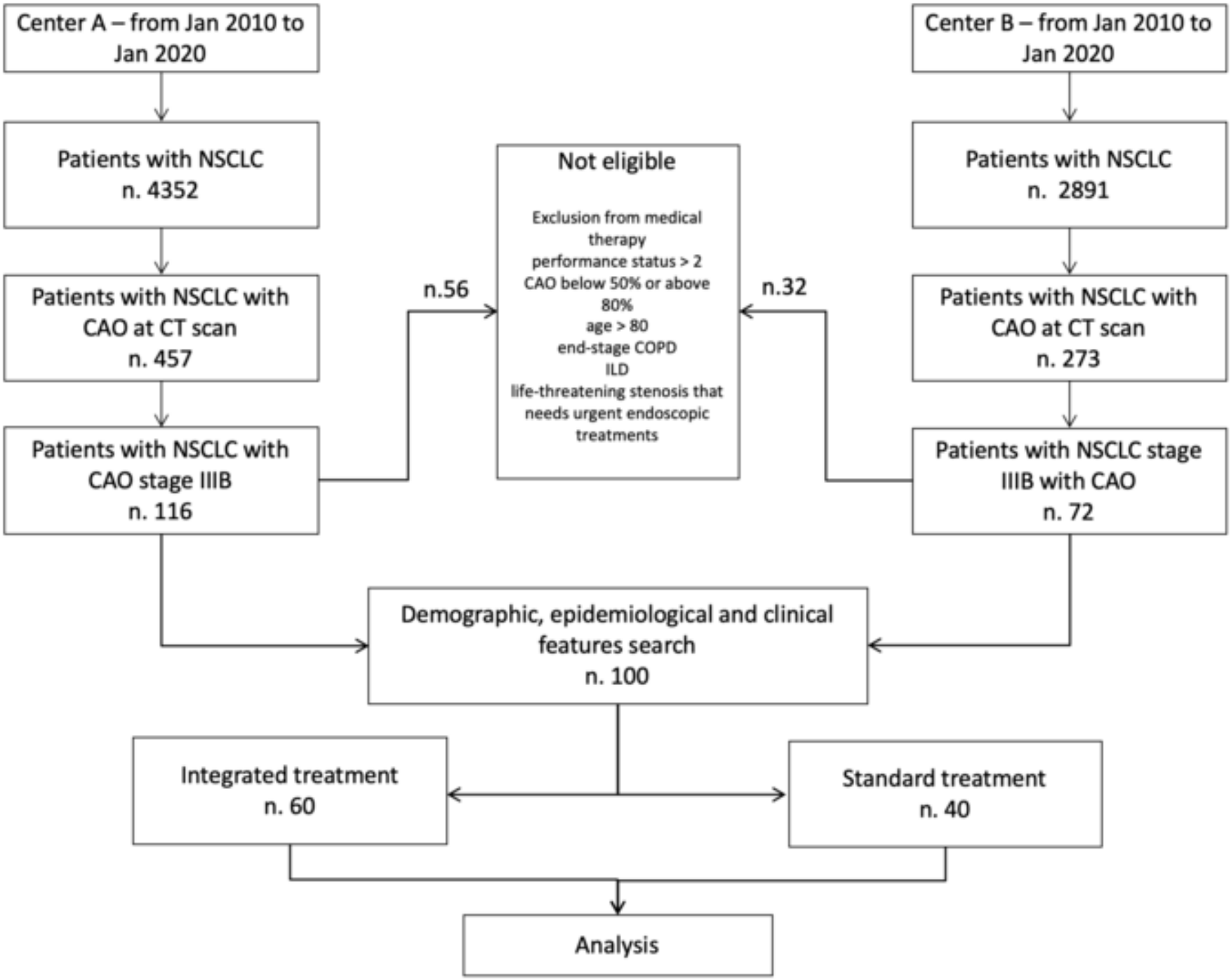
Logrank p=0.034
Integrated
Standard
0
5
10
12
Time (months)

Figure 1


Center A – from Jan 2010 to Jan 2020
Patients with NSCLC n. 4352
Patients with NSCLC with CAO at CT scan n. 457
Patients with NSCLC with CAO stage IIIB n. 116
n.56
Not eligible
Exclusion from medical therapy
performance status > 2
CAO below 50% or above 80%
age > 80
end-stage COPD
ILD
life-threatening stenosis that needs urgent endoscopic treatments
n.32
Center B – from Jan 2010 to Jan 2020
Patients with NSCLC n. 2891
Patients with NSCLC with CAO at CT scan n. 273
Patients with NSCLC stage IIIB with CAO n. 72
Demographic, epidemiological and clinical features search n. 100
Integrated treatment n. 60
Standard treatment n. 40
Analysis

Table

Table 1

Variable	Cohort			p value
	Total n=100	Integrated treatment n= 60	Standard care n=40	
Age, score (IQR)	74 (68-79.3)	73.3 (66.3-78.4)	76 (71-80.5)	n.s (0.2)
Male, n (%)	68 (68)	37 (62)	31 (78)	n.s. (0.1)
Charlson index, score (IQR)	5 (5-7)	5 (5-7)	5 (5-6)	n.s. (0.4)
Stenosis location				
Trachea, n (%)	21 (21)	16 (27)	5 (13)	n.s (0.1)
Main right bronchus, n (%)	60 (60)	35 (58)	25 (63)	n.s. (0.8)
Main left bronchus, n (%)	47 (47)	29 (48)	18 (45)	n.s. (0.8)
Carina, n (%)	17 (17)	15 (25)	2 (5)	0.01
Extensive involvement	17 (17)	15 (25)	2 (5)	0.01
Obstruction, % (IQR)	65 (60-75)	70 (65-75)	65 (65-75)	n.s. (0.29)
Histotype				
Adenocarcinoma, n (%)	28 (28)	13 (22)	15 (38)	n.s. (0.1)
Squamocellular carcinoma, n (%)	57 (57)	31 (53)	26 (65)	n.s. (0.2)
Others*, n (%)	15 (15)	11 (18)	4 (10)	n.s. (0.4)
Mutational status				
EGFR, n (%)	12 (12)	9 (15)	3 (8)	n.s. (0.4)
KRAS, n (%)	21 (21)	12 (20)	9 (23)	n.s. (0.8)
BRAF, n (%)	0 (0)	0 (0)	0 (0)	n.s. (0.9)
ALK, n (%)	2 (2)	0 (0)	2 (5)	n.s. (0.2)
PDL1***, n (%)	14 (14)	9 (15)	5 (13)	n.s. (0.8)
Treatment				
Traditional CHT/RT, n (%)	90 (90)	55 (92)	35 (87.5)	n.s. (0.5)
TKI, n (%)	12 (12)	9 (15)	3 (8)	n.s. (0.4)
Immunotherapy, n (%)	17 (17)	11 (18)	6 (15)	n.s. (0.8)

Demographic and clinical characteristics of the general population and on the basis of treatment. The data are presented as a numerical a nd percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for $p<0.05$.* Others includes NOS (n=10) and large cells carcinoma (n=5).** *PDL-1 is referred to patients with a PDL-1 expression above 50%. ~~PDL-1 feature is referred to patients with a PDL-1 expression above 50%.~~

IQR = interquartile ranges; EGFR = epidermal growth factor receptor; BRAF = v-raf murine sarcoma viral oncogene homolog B1; KRAS = Kirsten rat sarcoma; ALK = Anaplastic lymphoma kinase; PDL1 = programmed death-ligand 1; CHT = chemotherapy; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

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Table

Table 2

Feature	
Stenting procedure, n (%)	54 (90)
Type of stent	
Y, n (%)	24 (40)
Single, n (%)	34 (60)
Obstruction removal, n (%)	35 (58)
Type of obstruction removal, n (%)	
Laser, n (%)	6 (17)
Mechanical, n (%)	16 (46)
Laser + mechanical, n (%)	13 (37)
Complications at 1-year	10 (19)
Post-obstructive pneumonia, n (%)	5 (9)
Granulation, n (%)	8 (15)
Dislocation, n (%)	8 (15)
Removal, n (%)	9 (17)
Occlusion, n (%)	6 (20)

Technical endoscopic features and clinical events of patients that underwent integrated treatment. Data are presented as number and percentage.

Six patients presented occlusion, further dislocation and subsequent removal of the stent; of them 5 patients presented post-obstructive pneumonia; two patient presented granulation and one of them underwent stent removal; two patients presented dislocation without occlusion and were further subjected to removal.

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Table

Table 3

	Unadjusted and adjusted relative hazards of 12 months survival			
	Unadjusted HR (95%CI)	**p value**	**Adjusted* HR (95%CI)**	**p value**
		All cases		
Standard care	1		1	
Integrated care	2.1 (1.1-4.8)	0.003	1.9 (1-3.8)	0.02
		Stratum % obstruction below 65 %		
Standard care	1		1	
Integrated care	1.5 (0.6-4)	0.3	1.4 (0.6-3.7)	0.4
		Stratum % obstruction above 65 %		
Standard care	1		1	
Integrated care	4.1 (1.3-12.7)	0.01	3.7 (1.1-11.8)	0.01
		Stratum mutational status KRAS+		
Standard care	1		1	
Integrated care	8.3 (1.6-49)	<0.001	5.5 (1.2-15)	0.02
		Stratum mutational status KRAS-		
Standard care	1		1	
Integrated care	1.6 (0.67-4.1)	0.27	1.5 (0.6-4.5)	0.3
		Stratum left bronchus involvement+		
Standard care	1		1	
Integrated care	1.8 (0.65-5.2)	0.23	1.9 (0.7-6)	0.2
		Stratum left bronchus involvement-		
Standard care	1		1	
Integrated care	3.2 (1.1-9.8)	0.03	3.4 (1.2-11.2)	0.02

Hazard ratios from fitting a standard Cox regression model
*Adjusted for carina and extensive involvement

Table

Table 4

Outcome	Cohort			OR	p-value
	Total n=100	Integrated treatment n=60	Standard care n=40		
Atelectasis, n (%)	28 (28)	11 (18.3)	17 (42.5)	0.3 (0.12-0.76)	0.01
Rehospitalization, n (%)	34 (34)	15 (25.9)	26 (47.5)	0.4 (0.17-0.9)	0.03
Infectious event, n (%)	28 (28)	18 (30.5)	10 (25)	1.3 (0.5-3.4)	n.s. (0.7)
Haemorrhagic event, n (%)	23 (23)	13 (21.7)	10 (25)	0.8 (0.3-2.1)	n.s. (0.8)
Respiratory failure, n (%)	30 (29)	14 (23.3)	16 (40)	0.46 (0.2-1.1)	n.s (0.1)
Palliative treatments, n (%)	31 (31)	16 (26.7)	15 (37.5)	1.1 (0.25-1.4)	n.s. (0.9)
Symptoms-free time, months (IQR)	2.5 (1-5)	4 (2-6)	2 (1-4.5)	0.4 (0.15-0.8)	0.02

Clinical outcome for the general population and according to treatment received. The data are presented as a numbers and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for $p<0.05$.

OR = odds ratio; IQR = interquartile range

Table S1

Treatment	Cohort			p value
	Total n=90	Integrated treatment n= 55	Standard care n=35	
Pemetrexed/carboplatin, n (%)	43 (48)	26 (47)	17 (49)	n.s. (0.9)
Pemetrexed/cisplatin, n (%)	28 (31)	18 (33)	10 (29)	n.s. (0.8)
Gemcitabine/carboplatin, n (%)	12 (13)	7 (13)	5 (14)	n.s. (0.9)
Gemcitabine/cisplatin, n (%)	3 (3)	2 (4)	1 (3)	n.s. (0.9)
Placlitaxel/carboplatin, n (%)	4 (4)	2 (4)	2 (6)	n.s. (0.6)

Demographic and clinical characteristics of the general population and on the basis of treatment. The data are presented as a numerical and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for $p<0.05$.

IQR = interquartile ranges; EGFR = epidermal growth factor receptor; BRAF = v-raf murine sarcoma viral oncogene homolog B1; KRAS = Kirsten rat sarcoma; ALK = Anaplastic lymphoma kinase; PDL1 = programmed death-ligand 1; CHT = chemotherapy; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

Table 2

Symptom*	Cohort			p value
	Total n=100	Integrated treatment n= 60	Standard care n=40	
Dyspnea, n (%)	25 (25)	14 (23)	11 (28)	n.s. (0.6)
Persistent cough, n (%)	21 (21)	12 (20)	9 (23)	n.s. (0.8)
Hemoptysis, n (%)	10 (10)	5 (8)	5 (13)	n.s. (0.5)
Wheezing, n (%)**	7 (7)	5 (8)	2 (5)	n.s. (0.5)
No symptoms, n (%)	37 (38)	24 (40)	13 (33)	n.s. (0.4)

Symptoms of the general population and on the basis of treatment. The data are presented as a numerical and percentage. The statistical significance was set for $p<0.05$. ** "Symptom" is intended as the main reported clinical manifestation. ** "Wheezing" is intended as any respiratory sounds suggestive for airway lumen narrowing.*

Table 2

Variable	Cohort				p value
	Total n=60	Debulking alone n= 6	Stenting alone n=25	Both procedures n=29	
Death at 12 months, n (%)	13 (21.6)	3 (50)	5 (20)	5 (17.2)	n.s (0.2)
Atelectasis, n (%)	11 (18.3)	3 (50)	4 (16)	4 (13.8)	n.s. (0.1)
Rehospitalization, n (%)	15 (25.9)	5 (83.3)	6 (24)	4 (13.8)	0.002
Infectious event, n (%)	18 (30.5)	4 (66.7)	6 (24)	8 (27.6)	n.s. (0.1)
Hemorrhagic event, n (%)	13 (21.7)	2 (33.3)	4 (16)	7 (24.1)	n.s. (0.6)
Respiratory failure, n (%)	14 (23.3)	5 (83.3)	6 (24)	3 (13.8)	0.001
Palliative treatments, n (%)	16 (26.7)	3 (50)	5 (20)	8 (27.6)	n.s. (0.3)
Overall survival, months (IQR)	23.7 (8.7-40)	18.5 (8.2-31.3)	24.2 (10.2-37.4)	25.2 (11.3-41)	n.s. (0.47)
Symptoms-free time, months (IQR)	4 (2-6)	2.5 (2-3.3)	3.3 (2.4-5.3)	4.7 (3.2-6)	0.04

Clinical outcome for patients undergoing integrated treatment and according to specific treatment received. The data are presented as a numbers and percentage value for dichotomic variables and as median and interquartile ranges for continuous variables. The statistical significance was set for $p<0.05$.

IQR = interquartile range

Integrated intErventional bronchoscopy in the treatment of locally adVanced non-small lung cancER with central Malignant airway Obstructions: a multicentric REtrospective study (EVERMORE)

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Author contribution

AM and DA have made substantial contributions to conception of the study, therefore they should both be considered as first authors. NF, RP, AA, ST, EC, FF, GFC and EM reviewed the literature, wrote the manuscript and produced the figures. MD, MB, FB, FG and GB reviewed the literature and wrote the manuscript. RF, LC and IC designed the study, elaborate data and wrote the manuscript. RT designed the study, performed the analysis, wrote and reviewed the manuscript. EC reviewed and edited the manuscript. All authors have made substantial contributions to the conception, design and realization of the study.