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The interplay between endoscopists and clinicians: clinical significance and outcomes of a multi-modal evaluation and treatment of benign and malign airway diseases

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Index

Abstract

The interplay between endoscopists and clinicians: clinical significance and outcomes of a multi-modal evaluation and treatment of benign and malign airway diseases.

As real-life management of airway neoplastic and non-neoplastic diseases results challenging for clinicians, the optimal approach is supposed to be multimodal and multidisciplinary. This is due to the heterogeneous nature of the pathological processes underlying airways involvement. There are benign and malignant lesions, but also dynamic lesions, that can cause obstruction of the airways, with a wide range of respiratory symptoms and different clinical severity. The endoscopic approach to airways obstructive lesions has been confirmed to be important for the proper treatment of these patients. First, this applies to the management of life-threatening complications. Secondly, it allows restoring airway patency, and may be used for diagnostic purposes. Finally, the optimization of an integrated approach based on endoscopic and medical techniques can represent an effective strategy to improve diagnosis, survival and quality of life of patients with clinically relevant airway diseases. The aim of this research project was to explore the clinical significance and the related outcomes of a multi-modal approach including surgical, endoscopic, and medical treatment across a spectrum of different airways diseases. The research question has been addressed by means of four clinical studies.

The first retrospective, multicentre, cohort study was carried out in two teaching hospitals over a 10 years period, enrolling patients with age >18 years, histologic diagnosis of NSCLC at stage IIIB and CAO at onset of disease and performance status < 2. Primary outcome was 1-year survival. The onset of significant respiratory events, hospitalization, need for palliative treatments, symptoms-free interval and overall survival served as secondary outcomes. We showed that the integration of interventional bronchoscopy in the management of locally advanced NSCLC with CAO, especially when proposed early, not only has a palliative purpose but also has a significant impact on the patient's prognosis, showing a clear 1-year survival advantage for the same stage of disease. Moreover, we have shown that greater gain in life expectancy is closely related to anatomical (airway occlusion> 65%, no left mainstem obstruction) and molecular (KRAS-mutant NSCLC) cancer features. A post-hoc analysis of this cohort of patients focusing on those with primary tracheal tumors constituted the fourth study. In this line, we showed that multimodal

treatment including interventional bronchoscopy and associated radiotherapy for unresectable primary tracheal tumors seems feasible and may provide benefits in terms of survival especially for patients with cystic-adenoid histology.

The second study was a retrospective, observational cohort study carried out at the University Hospital of Modena (Italy) in two departments of Bronchoscopy Unit and Otolaringology Unit. We compared two different endoscopic techniques to restore tracheal patency in benign tracheal stenosis not eligible for surgery: balloon dilatation (BA) through laryngoscopy, and tracheal stenting (ST) with rigid bronchoscopy. Patients were considered to be "stabilized" (primary outcome) if they did not report significant respiratory symptoms, or restenosis in the long-term (2 years) following the endoscopic procedures. We concluded that ST seems to be more effective in achieving stabilization of tracheal patency in complex benign tracheal stenosis when compared with BA, although burdened with a significantly higher number of adverse effects.

As regards the third study, patients with a diagnosis of sovra-glottic cancer with at least a 5-years follow-up were retrospectively considered eligible for enrolment. We excluded patients with presence of distal metastasis at the time of diagnosis and presence of a synchronous cancer. All demographic and clinical variables (including HPV infection, TNM classification, treatment received, response and disease relapse) were collected, to evaluate the association between them and the onset of distal metastasis. The study confirmed that a significant number of patients with local sovra-glottic cancer may develop distal metastasis despite treatment during follow-up. Smoking status, advanced malignant disease at the time of diagnosis, and poor response to treatment were independent factors associated with this late event. The metastatic dissemination significantly reduced survival but only in those patients who did not have HPV infection. The early phenotyping of patients at major risk of late metastasis onset might improve the clinical management and the follow-up of these patients.

In conclusion, with the first and the second study we have showed that a multi-modal approach may represent the optimal choice of treatment for malignant obstructive lesions of the central airways and for benign tracheal stenosis. The results of third study have suggested that a multidisciplinary evaluation of patients with upper malignant airway diseases may allow identifying those at major risk for disease progression despite surgical and medical treatment.

Sinossi

L'interazione tra endoscopisti e clinici: significato clinico e risultati della valutazione multimodale e trattamento di malattie benigne e maligne delle vie aeree.

Poiché la gestione delle malattie delle vie aeree risulta difficile per i clinici, l'approccio ottimale dovrebbe essere multimodale. Ciò è dovuto all'eterogeneità delle patologie delle vie aeree: lesioni benigne, dinamiche e maligne possono causare ostruzione delle vie aeree, con una vasta gamma di sintomi respiratori e gravità clinica.

L'approccio endoscopico alle lesioni ostruttive delle vie aeree si conferma essere importante per il trattamento adeguato di questi pazienti, in primis per la gestione delle complicazioni letali. In secondo luogo consente di ripristinare la pervietà delle vie aeree. Infine l'ottimizzazione di un approccio integrato può rappresentare una strategia efficace per migliorare la diagnosi, la sopravvivenza e la qualità della vita di questi pazienti.

Lo scopo di questo progetto di ricerca è quello di esplorare il significato clinico e i risultati di un approccio multimodale che include trattamenti chirurgici, endoscopici e medici in diverse malattie delle vie aeree, attraverso quattro studi clinici.

Il primo studio ha arruolato pazienti con la diagnosi di NSCLC in fase IIIB e CAO all'inizio della malattia. L'esito primario era la sopravvivenza a 1 anno. Abbiamo dimostrato che l'integrazione della broncoscopia interventistica, soprattutto quando proposto precocemente, non solo ha uno scopo palliativo, ma ha anche un impatto significativo sulla prognosi del paziente, con un chiaro vantaggio di sopravvivenza a 1 anno per lo stesso stadio della malattia. Inoltre, abbiamo dimostrato che un maggiore aumento dell'aspettativa di vita è correlato alle caratteristiche anatomiche e molecolari del cancro. Una analisi post-hoc della popolazione di questo studio con focus su pazienti con tumore primitivo della trachea ha costituito il quarto studio. In esso abbiamo dimostrato come una terapia multimodale integrante trattamento endoscopico e radioterapia sia fattibile e possa portare a benefici in termini prognostici soprattutto per quei pazienti con tumore primitivo della trachea di tipo adenoido-cistico.

Il secondo studio è stato condotto in due dipartimenti di broncoscopia e di otorinolaringoiatria. Abbiamo confrontato due tecniche endoscopiche per ripristinare la pervietà tracheale nelle stenosi tracheali benigne non candidabili alla chirurgia: dilatazione con balloon (BA) attraverso

laringoscopia e stenting tracheale (ST) con broncoscopia rigida. I pazienti sono stati considerati "stabilizzati" (outcome primario) se non riportavano sintomi respiratori significativi o re-stenosi nei 2 anni successivi alle procedure. ST sembra essere più efficace nel raggiungere la stabilizzazione della pervietà tracheale nelle stenosi tracheali benigne complesse rispetto a BA, anche se è gravato da un maggior numero di effetti avversi.

Per il terzo studio pazienti con una diagnosi di cancro sovraglottico con almeno 5 anni di follow-up sono stati considerati arruolabili, escludendo pazienti con metastasi a distanza al momento della diagnosi o con presenza di cancro sincrono. Tutte le variabili demografiche e cliniche sono state raccolte per valutare l'associazione tra esse e l'esordio di metastasi. Lo studio ha confermato che un numero significativo di pazienti con tumore sovraglottico locale può sviluppare metastasi nonostante il trattamento durante il follow-up. Il fumo, lo stadio avanzato al momento della diagnosi e la scarsa risposta al trattamento erano fattori indipendenti associati a questo evento tardivo. La diffusione metastatica ha ridotto significativamente la sopravvivenza, ma solo in quei pazienti che non avevano infezione da HPV. La fenotipizzazione precoce dei pazienti a maggiore rischio di insorgenza di metastasi tardiva potrebbe migliorare la gestione clinica e il follow-up di questi pazienti.

In conclusione, con il primo e il secondo studio abbiamo dimostrato che un approccio multimodale può rappresentare la scelta ottimale di trattamento per le lesioni ostruttive maligne delle vie aeree centrali e per la stenosi tracheale benigna. I risultati del terzo studio hanno suggerito che una valutazione multidisciplinare dei pazienti con malattia delle vie aeree maligne superiori può consentire di identificare quelli a rischio maggiore di progressione della malattia, nonostante il trattamento chirurgico e medico.

General introduction

A real-life management of airway neoplastic and non-neoplastic diseases can be very challenging for clinicians. Consequently, the optimal approach is supposed to be multimodal and multidisciplinary, including a huge number of specialists like endoscopists, surgeons, radiologists, and other disciplines. This is due to the heterogeneous nature of the pathological processes underlying airways involvement. There are benign and malignant lesions, but also dynamic lesions, as well as primitive or secondary, that can cause obstruction of the airways. As a consequence, a wide range of respiratory symptoms and different clinical severity are expected.

The endoscopic approach to airways obstructive lesions has been confirmed to be important for the proper treatment of these patients. First, this applies to the management of life-threatening complications. Secondly, it allows restoring airway patency, and may be used for diagnostic purposes. The initial bronchoscopy is mostly diagnostic and used to plan further interventions. During bronchoscopy lesions can be assessed visually, distal secretions suctioned, and diagnostic tissue obtained, if feasible. In some patients, bronchoscopy can be both diagnostic and therapeutic, considering in particular rigid bronchoscopy and its guarantee to secure the airway (e.g., foreign body retrieval, coring) (1). Finally, the optimization of an integrated approach based on endoscopic and medical techniques can represent an effective strategy to improve diagnosis, survival and quality of life of patients with clinically relevant airway diseases.

Central Airway Obstructions

Airway management is an essential skill for clinicians caring for critically ill or injured patients and is fundamental to the practice of emergency medicine, where an endoscopic guide can be crucial for intubating trachea (2).

Considering life-threatening obstructions, once the airway is secured and adequate gas exchange is documented, a bronchoscopic inspection is indicated in order to elucidate a likely etiology of the central airway obstruction (CAO). Bronchoscopy should be done either immediately (e.g., foreign body or almost complete occlusion of the airway) or within the first 12 to 24 hours (e.g., high grade occlusion in an otherwise stable, ventilated patient).

Central airway obstruction refers to the obstruction of air flow in the trachea and mainstem bronchi, and it can be due to several malignant and non-malignant processes. Primary lung cancer

is the most common cause of malignant CAO. Secondly, other neoplastic processes, both primitive and metastatic, may be the cause of obstruction. Although squamous cell lung cancer more commonly affects the major airways than adenocarcinoma, both forms of Non Small Cell Lung Cancer (NSCLC) can present with CAO (3). Airway obstruction occurs via direct compression by or extension from a parenchymal tumor into the airway lumen, or via direct or metastatic involvement of the airway by tumor. Airway obstruction complicates approximately 20 to 30 percent of patients with lung cancer, causing symptoms like shortness of breath or atelectasis, although not all reported cases are associated with central airway obstruction (4). Some studies show that in advanced lung cancer, CAO is associated with poor survival when adjusted for age, gender and stage of cancer (5). In addition, more than 40% of deaths due to pulmonary neoplastic pathologies can be attributed to locoregional diseases (6).

As regards non-malignant CAO, common conditions are foreign body aspiration and tracheobronchomalacia, as well as iatrogenic tracheal strictures due to endotracheal or tracheostomy tubes or anastomotic stenoses following lung transplant.

The clinical manifestations of central airway obstruction typically depend upon the degree of luminal narrowing, as well as the location and length of time that obstruction has been present. When the lumen of the trachea is narrowed to less than 8 mm of diameter, the dyspnoea typically develops under effort, while a decrease to less than 5 mm leads to the appearance of dyspnoea even at rest. In case of fixed airway obstruction, dyspnoea and wheezing are usually not responsive to bronchodilator and anti-inflammatory therapy, so failure of these therapies should give the clinician reason to suspect the presence of a CAO (7). Symptoms of CAO, whatever their etiology, may range from mild dyspnoea to life-threatening respiratory failure; the so-called “syndrome of CAO” is usually due to an occlusion of >50% of the trachea, mainstem bronchi, bronchus intermedius or a lobar bronchus. Other common features are cough, hemoptysis, and wheeze. Many of these patients are misdiagnosed as suffering from an exacerbation of asthma or COPD, or as having bronchitis or pneumonia. In contrast, the demonstration of acute inspiratory stridor and respiratory distress in an at-risk patient are worrisome signs of CAO that should prompt immediate diagnostic evaluation and therapeutic interventions.

When central airway obstruction is suspected, a multidisciplinary approach in a centre with expertise in airway management is advisable. However, transfer to a specialized centre should not delay life-saving therapies. There are several endoscopic therapeutic options for recanalizing or

stabilizing the airway, concerning intrinsic obstruction, extrinsic compression, and dynamic collapse (8). In most cases, flexible bronchoscopy with or without endobronchial ultrasound (EBUS) is sufficient for the diagnostic evaluation of non-life-threatening central airway lesions. This includes visual inspection for the extent and nature of the obstruction (e.g., intrinsic versus extrinsic obstruction, involvement of the oropharynx, carina, or distal bronchi), the identification of unexpected distal airway involvement, the safe acquisition of tissue when indicated, and planning for additional interventions, if needed (9).

Once obtained the initial assessment and diagnosis, the goals of treatment are airway patency and symptom palliation which are usually performed by debulking or removing the obstruction, and/or by stenting an airway such that patients can safely breathe spontaneously. In most cases, this is achieved bronchoscopically, but occasionally surgery is required. Although there are an increasing number of bronchoscopic therapies available to locally treat lung cancer involving the central airway, patients should be primarily treated according to the appropriate stage using a multidisciplinary approach that involves pulmonologists, surgeons, radiotherapists, and oncologists (10). Multimodality approaches featuring a combination of several bronchoscopic interventions (e.g., laser resection plus stenting) are often preferred by experts for their mucosal sparing effects and long-term success in achieving patency (11). Choosing among the interventions is dependent upon factors including the cause of the lesion, predicted response to therapy, operator experience, available expertise, patient prognosis or health status, patient preference, and the ability of the patient to tolerate a selected procedure (12-13).

Laser, electrocautery, and argon plasma coagulation are used for immediate relief from obstruction due to intraluminal tumors, while brachytherapy, photodynamic therapy, and cryosurgery are delayed in their effects and cannot be used for this purpose. Brachytherapy can be used for cancers that cause extrinsic compression. Laser therapy is an immediate-acting therapy with excellent debulking capacity, best suited to treating patients with intraluminal tumors causing CAO, as well as those associated with bleeding. As regards mechanical dilation, this approach is sometimes used via flexible or rigid bronchoscopy in patients with short cancerous lesions of the airway, but also it is also commonly used for benign stenoses. Although dilation is immediately effective, the results for neoplastic stenosis are usually not sustained, especially for lesions causing external airway compression. In addition, mucosal disruption from dilation may produce granulation tissue and accelerate recurrent stenosis, therefore other techniques including laser,

radiation, and/or stenting are often simultaneously used to maintain a patent airway. During rigid bronchoscopy, the endoscope is advanced through the stenotic airway opening and the barrel is then pushed through the obstruction in a rotating motion ("coring"). It is important to know what lies distal to the obstruction in order to not injure the airway with the rigid bronchoscope; however, with the rigid bronchoscope airway control is ensured and bleeding is usually minimal. In less severe cases, sequential balloon dilation (flexible bronchoscopy) or sequential rigid dilators (rigid bronchoscopy) may be used (14-15).

While dilation is often immediately effective but its effect is time-limited, stenting placement is usually performed following locally ablative or dilation therapies to prevent re-occlusion after patency has been restored. Airway stents can be utilized for both intrinsic and extrinsic lesions and require an assurance that the distal airway is patent. Dumon stent is currently the most widely used in the world for its properties and ease of use. It can be straight or Y bifurcated, for stenoses involving tracheal carina. There are however metal and silicone stents. The metal ones, usually made of nitinol, can be uncovered or covered with silicone or polyurethane; the latter are the most suitable for malignant CAO, but they are usually difficult to remove, once placed. Silicone stents instead are flexible and they can be easily removed, but migration is more common (16). They require introduction with a rigid bronchoscope and are definitely preferred in patients with cancer. However, re-stenosis is common because tumors or granulation tissue frequently grow into the stent. Moreover, a follow-up with multiple bronchoscopies is required for the detection of complications like stent displacement or atelectasis following obstruction. (17). Nowadays an ideal stent, which is biologically inert, easy to place and remove, resistant to compressive forces and at the same time not harmful to airway integrity, able to restore the airway patency and promote the correct clearance of secretions, does not yet exist.

Following the application of one or more of the endoscopic techniques to restore the airway patency, patients should be assessed clinically for resolution of symptoms. They should also usually repeat chest computed tomogram and bronchoscopic evaluation to visually assess the response to treatment. The optimal time and tool for follow-up assessment is unknown; also in this case a multidisciplinary discussion is fundamental to obtain the best management care.

In locally advanced NSCLC, usual therapeutic approach consists of a combination of local therapy (radiotherapy) with systemic platinum-based doublet chemotherapy. In recent years, the introduction of target therapy and immune-checkpoint inhibitors opened up new perspectives of

treatment. 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 (18–19). Despite this new therapeutic perspective, a group of these patients already presents at diagnosis with an occlusion of the central airways which can result in worse life expectancy.

Particularly 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 (20–21). 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 (22).

To date, there is currently no reliable evidence regarding the impact of interventional bronchoscopy on survival in locally advanced NSCLC (23).

Benign Tracheal Stenosis

Among the non-malignant causes of central airway obstruction, the most frequent are those of iatrogenic origin: considering the increased use of invasive mechanical ventilation procedures, the endotracheal intubation, tracheotomy packing or surgery may result in stenosis due to granulation tissue, especially at the level of the glottis, the subglottic space, or the trachea (24). Although the aetiology of benign laryngotracheal stenosis (LTS) is mainly iatrogenic, autoimmune diseases can also be associated with subglottic mucosal inflammatory changes resulting in central airway stenosis (including granulomatosis with polyangiitis, relapsing polychondritis, sarcoidosis and IgG4-related disease) (25).

The understanding of the pathophysiology of LTS is still an ongoing process and is crucial to develop new more effective therapeutic strategies. Until recently the laryngotracheal scar resulting from airway injury was considered an inert tissue requiring surgical removal to restore airway patency. This assumption has now been revised: tracheal scarring is seen as a fibroinflammatory event triggered by immunological alterations (25). Studies in animal models helped clarifying molecular, immunological, and genetic aspects that may play a role in the development of airway stenosis and in the healing process of the laryngeal-tracheal area. Recent

acquisitions suggest that different factors, such as growth factors, cytokines, altered fibroblast function and genetic susceptibility, can all interact in a complex way leading to aberrant and fibrotic wound healing after an insult that acts as a trigger. Also mechanisms like biomechanical stress and mechano-transduction activation could play a role in promoting dysregulated response to laryngo-tracheal mucosal injury (26).

Clinically, the management of symptomatic disease varies greatly depending on the underlying condition. Targeted treatment of the underlying etiology and restoration of airway patency to alleviate symptoms are the fundamental principles guiding the management of these pathologies. Severe LTS results in respiratory functional impairment, often challenging to be managed appropriately. The optimal treatment remains unknown; further, the prevention of LTS and its recurrence represents an important clinical need. The identification of the etiology of stenosis could be a critical factor for the long-term success of endoscopic treatment, although currently only a few studies have investigated the relationship between causes of tracheal stenosis and relapse after endoscopic surgery.

No data are currently available to help physicians choosing the most appropriate intervention, considering the clinical and anatomical characteristics of the stenosis. In addition, there are no widely accepted standardized therapeutic approaches, such as choice of bronchoscopic technique or when to refer for surgical management. A multidisciplinary approach - including evaluation by and discussion amongst interventional pulmonary, otolaryngology head and neck surgery, and thoracic surgery experts – is recommended. As such, each centre uses the endoscopic treatment based on the operator's experience.

Laryngotracheal surgery may be considered the treatment of choice, despite the intrinsic limitations related to the surgical procedure itself and/or the patient’s clinical status (27). Surgical resection in patients with autoimmune disease is rarely performed due to the concern of anastomotic complications (28-29).

Recently, less invasive techniques such as endoscopy are becoming increasingly relevant, even if burdened by frequent relapses requiring re-operation (30).

The two principal endoscopic techniques adopted to restore the tracheal patency are laryngoscopy with balloon dilatation (BA), and tracheal stenting (ST) with rigid bronchoscopy. However, the comparison between the two techniques on long-term results has never been evaluated.

Furthermore, lasers therapy is often used in the treatment of pathogenic airway processes in association with these techniques, but it is still unclear whether the potential tissue laser-injury can accelerate stenosis recurrence.

Upper Malignant Airway Diseases

Most of the upper malignant airway diseases begin from the mucosal surfaces, and they are predominantly squamous cell carcinomas. As malignant sovra-glottic pathologies falls into a wide and heterogeneous field, it may be potentially useful to divide the upper airway tumors into those affecting various anatomic subregions (31). More specifically, the anatomy of larynx can be considered crucial when considering the best management of laryngeal cancer, since the glottic, supraglottic or subglottic location can be a determining factor in deciding the best management strategy. The ideal treatment also varies depending on the stage of the disease (32).

Usually, a combination of surgery, radiotherapy and chemotherapy is generally required to optimize the chances for long-term disease control. The choice of therapy is typically based upon the specific site and its requirements, the surgical accessibility of the tumor, and the functional outcomes and morbidity associated with each modality. Radiotherapy and surgery result in similar rates of local control and survival for many sites. Decisions about the optimal sequencing and selection of surgery, radiotherapy and/or chemotherapy require multidisciplinary input. Definitely, key factors to consider include the primary tumor site and disease extent, the individual patient factors (age, comorbidity, preferences regarding treatment type), and the likely functional consequences and morbidity of each treatment approach. The choice of therapy should also take into account the experience and technology available at the patient's medical institution.

However, patients affected by a sovra-glottic cancer may experience the onset of distal metastasis despite effective and prompt treatment. Distant metastases in sovra-glottic carcinoma are rare, and when present most commonly involve the lung. (33). Presence of metastases was also reported in bone, liver, skin, brain, kidney and muscle (34).

Smoking is a primary factor that influences the risk of developing distal metastases (DM). It is also reported that the hazard of DM development increases by 1% per pack-year and patients with > 10 pack-years have a higher likelihood of locoregional failure and death (35). These considerations

could be explained by the fact that tobacco induces epigenetic alterations and can locally suppress local immunity that could interfere with tumor aggressiveness (36-37).

In addition to the traditional risk factors like smoking and alcohol consumption, HPV infection was found to play an important role in tumor pathogenesis of the upper airway (38). In addition, as regards oropharyngeal squamous cell carcinoma, patients without HPV infection seems to have a significantly higher risk of distant metastases (DMs) compared to HPV positive ones (39).

Ultimately, the risk factors associated with the development of metastasis have not been elucidated yet, being the role of human papillomavirus (HPV) still controversial. Moreover, while there is evidence that a metastatic disease is associated with worse overall survival, no data are available if a specific localization (e.g., lung) might affect the prognosis of these patients.

Aims and significance of the present research

The aim of this research project was to explore the clinical significance and the related outcomes of a multi-modal approach including surgical, endoscopic, and medical treatment across a spectrum of different airways diseases. The research question has been addressed by means of three clinical studies:

- In the first study, the main purpose is 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 locally advanced (stage IIIB) NSCLC with CAO.

- In the second one, given that there is no definitive consensus about the endoluminal treatment of benign tracheal stenosis (40), the aim is to compare the effectiveness of the two main endoscopic intervention methods (balloon dilation and stent placement) on the treatment of benign tracheal stenosis not eligible for open surgery.

- In the third study the objective is to compare 5-years overall survival in a population of patients with sovra-glottic airways cancer but not metastatic at the time of diagnosis, and also to evaluate risk factors for distal metastasis development, in order to explore the impact of HPV and the difference on survival according to the site of metastatisation.

- in the fourth study we wanted to explore the survival and the clinical factors influencing prognosis of patients with unresectable primitive tracheal tumor undergoing multimodal treatment integrating interventional bronchoscopy and radiotherapy.

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Chapter 1

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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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.

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 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. BTime 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**.

Figure 1

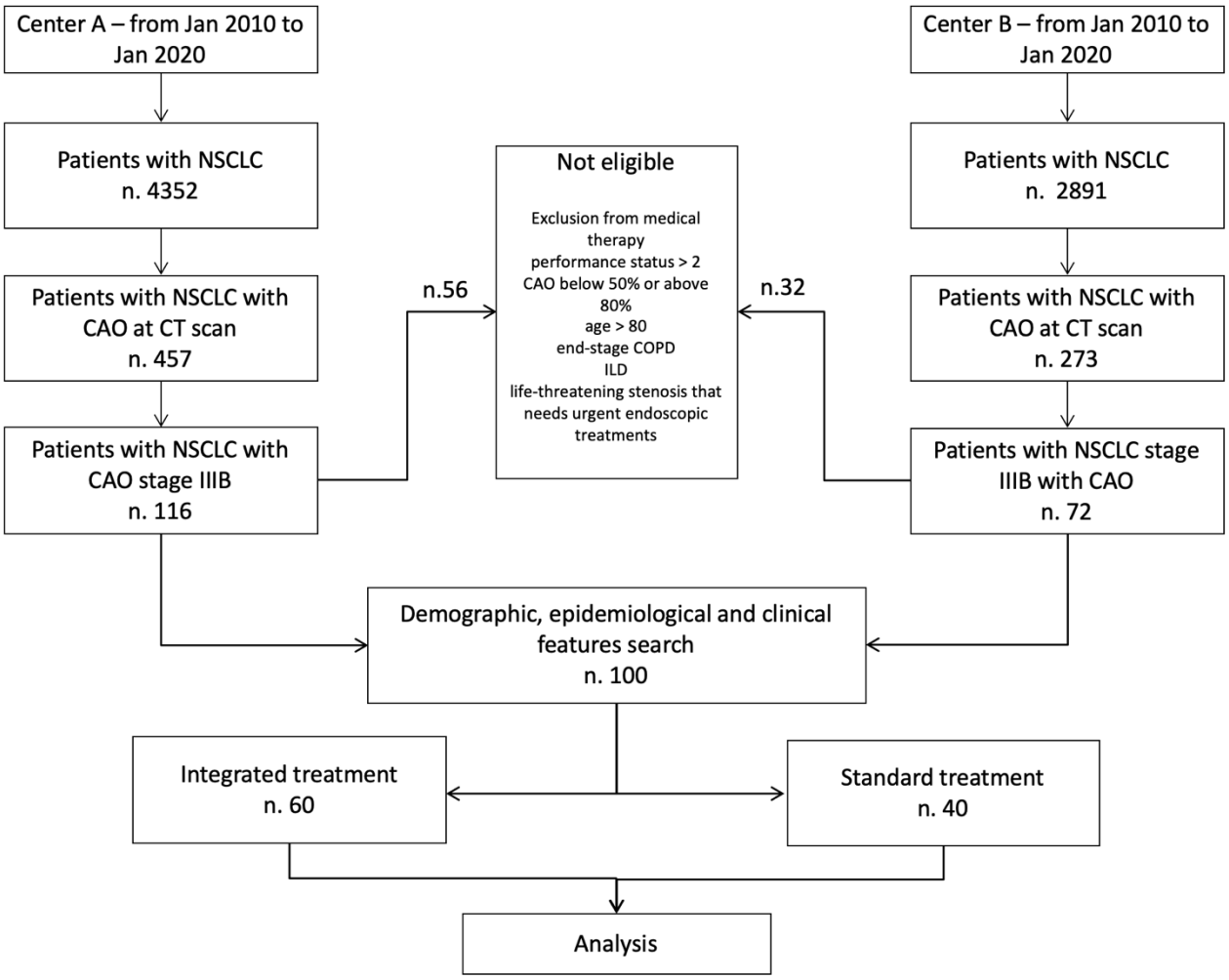

Fig. 1. Flow chart for patients in this study.

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.

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)

Table 1. 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 $p<0.05$.* Others includes NOS (n=10) and large cells carcinoma (n=5) ** PDL-1 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.

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**.

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)

Table 2. 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.

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.

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

Table 3. Hazard ratios from fitting a standard Cox regression model

*Adjusted for carina and extensive involvement

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 2**, 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**).

Figure 2

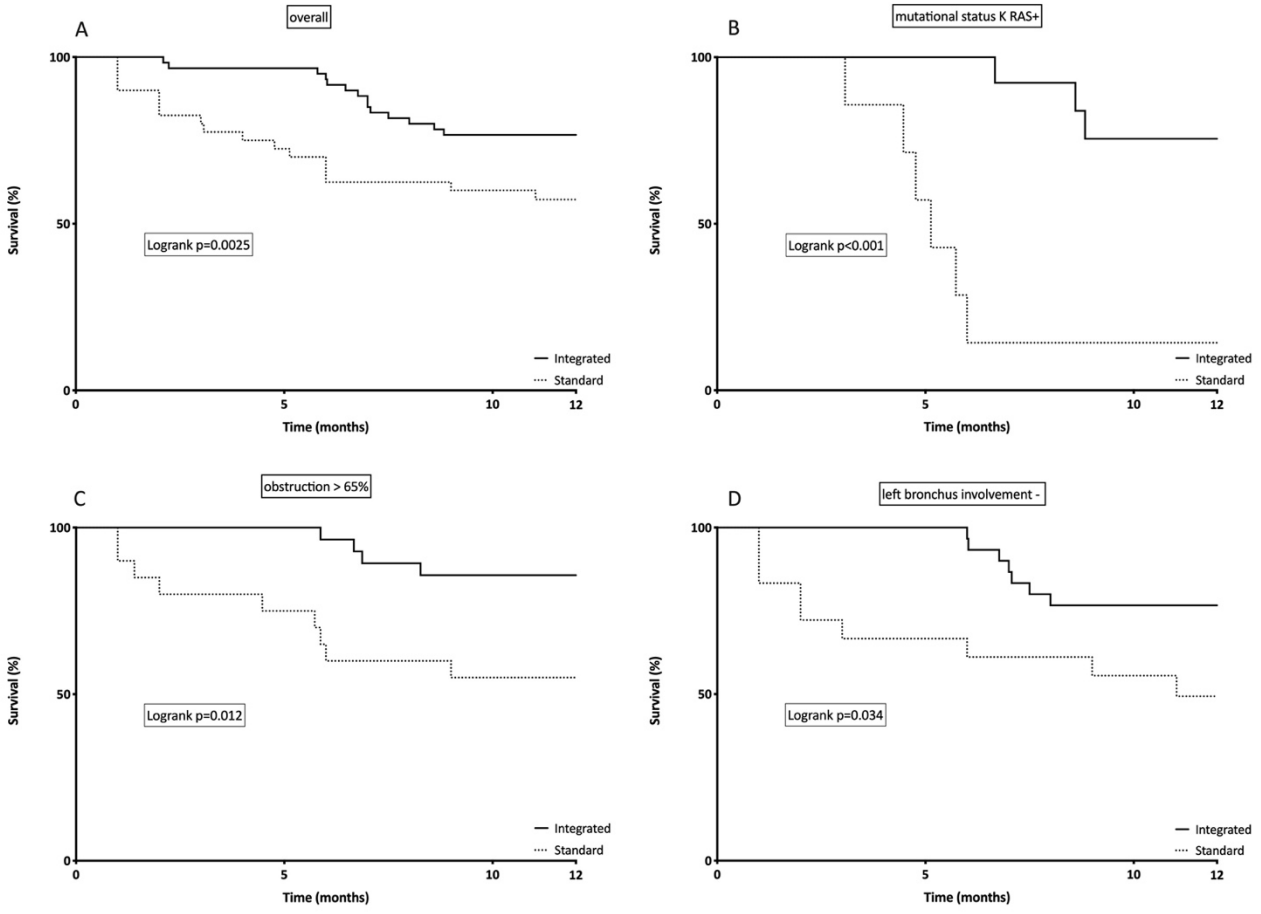

Fig. 2. Kaplan-Mayer curves showing impact of integrated treatment compared to standard therapy on 1-year survival for the overall population (panel A), for patients presenting K-RAS mutation (panel B), for patients with lumen occlusion > 65% (panel C) and for patients with lack of left bronchus involvement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

Figure 3

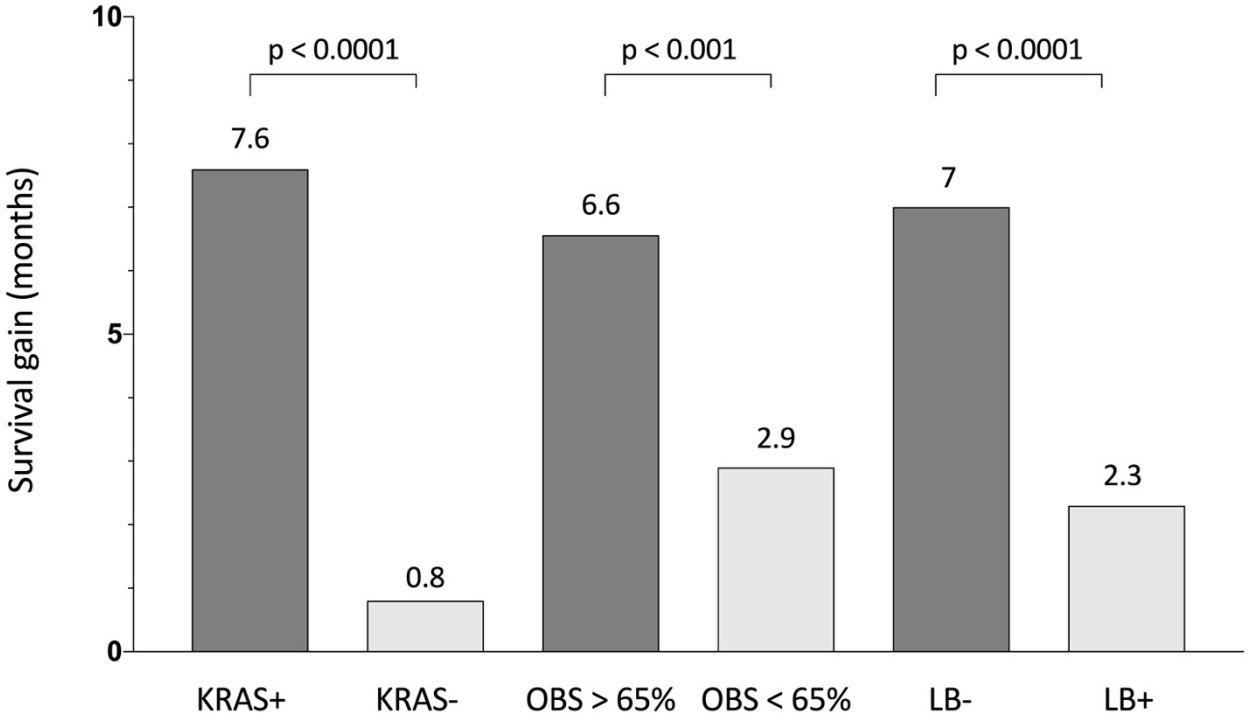

Fig. 3. Comparison of survival gain of integrated treatment over standard therapy for patients presenting K-RAS mutation (left side), for patients with lumen occlusion > 65% (central part) and for patients with lack of left bronchus involvement (right side).

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).

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

Table 4. 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

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 symptomatic 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.

Appendix – Supplementary materials

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)

Table S1. 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 S2

Symptom*	Cohort			
	Total n=100	**Integrated treatment n= 60**	**Standard care n=40**	**p value**
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)

Table S2. 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 S3

Variable	Cohort				
	Total n=60	Debulking alone n= 6	Stenting alone n=25	Both procedures n=29	p value
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

Table S3. 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

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Chapter 2

Stenting versus balloon dilatation in patients with tracheal benign stenosis – the STROBE trial

Marchioni A, Andrisani D, Tonelli R, Andreani A, Cappiello GF, Ori M, Gozzi F, Bruzzi G, Nani C, Feminò R, Manicardi L, Baroncini S, Mattioli F, Fermi M, Fantini R, Tabbì L, Castaniere I, Presutti L, Clini E. Stenting versus balloon dilatation in patients with tracheal benign stenosis: The STROBE trial. Laryngoscope Investig Otolaryngol. 2022 Feb 23;7(2):395-403. doi: 10.1002/lio2.734. PMID: 35434321; PMCID: PMC9008152.

Abstract

Background

It is well known that benign tracheal stenosis represents an obstacle to open surgery, and that its treatment could be challenging. Two endoscopic techniques have so far been adopted to restore tracheal patency: balloon dilatation (BA) through laryngoscopy, and tracheal stenting (ST) with rigid bronchoscopy.

The main objective of this study was to compare the efficacy of BA and ST to ~~cure~~ treat benign tracheal stenosis not eligible for surgery. We also compared the rate of adverse events in the two treatment groups.

Methods

A retrospective, observational cohort study was carried out at the University Hospital of Modena (Italy) from November 2012 to November 2017 in two separate departments. Patients were considered to be “stabilized” (primary outcome) if they did not report significant respiratory symptoms, or re-stenosis in the long-term (2 years) following the endoscopic procedure.

Results

Sixty-six patients were included in the study (33 in the BA and 33 in the ST group, respectively). Unadjusted Kaplan-Meier estimates showed a greater therapeutic effect of ST compared to BA at 2 years (HR=3.9 95%CI [1.5-9.8], p=0.01). After adjusting for confounders, stratified analyses showed that this effect was significant in patients with complex stenosis, idiopathic etiology, and degree of stenosis >70%. Compared with BA, ST showed a higher rate of adverse events (p=0.01).

Conclusions

Compared to balloon dilatation, tracheal stenting seems to be more effective in achieving stabilization of tracheal patency in complex benign tracheal stenosis, although burdened with a significantly higher number of adverse effects. These findings warrant future prospective study for confirmation.

Introduction

Benign tracheal stenosis represents a major therapeutic challenge whose optimal treatment remains unknown. Although surgery can be considered the treatment of choice, resection-anastomosis is often limited by the patient's condition, and the technical limits inherent to laryngotracheal surgery [1] .

In recent years, the role of endoscopic treatment of airway stenosis has been progressively increasing due to its limited invasiveness, even though this approach is burdened by frequent relapses [2]. Stanley Shapshay first described in 1987 the endoscopic technique that combines laser resection with rigid bronchoscopy dilation in the treatment of tracheal and subglottic scarring stenosis [3]. Lately, the endoscopic treatment of tracheal stenosis has evolved with the introduction of different techniques whose success is still debated [4–6]. Therefore, no data are currently available to help physicians choosing the most appropriate intervention depending on the clinical and anatomical characteristics of the stenosis. As such, each center uses the endoscopic treatment based on the operator's experience. In particular, two endoscopic techniques are frequently adopted to restore the tracheal patency: laryngoscopy with balloon dilatation, and tracheal stenting with rigid bronchoscopy. However, the comparison between the two techniques on long-term results has never been evaluated. Furthermore, lasers therapy is often used in the treatment of pathogenic airway processes, but it is still unclear whether the potential tissue laser-injury can accelerate stenosis recurrence.

Tracheal narrowing can be the result of an underlying heterogeneous mechanisms that involving mechanical (traumatic or iatrogenic), autoimmune or idiopathic causes. Surgical resection per se in patients with autoimmune disease is rarely performed due to the concern of anastomotic complications [7,8]. The identification of the etiology of stenosis could be a critical factor for the long-term success of endoscopic treatment, although currently only a few studies have investigated the relationship between causes of tracheal stenosis and relapse after endoscopic surgery.

Since there is no definitive or proven consensus about the endoluminal treatment of benign tracheal stenosis [9] , the purpose of this study is to compare the effectiveness of the two main endoscopic intervention methods (i.e., balloon dilatation and stent placement) on the treatment of benign tracheal not eligible for open surgery.

Materials and methods

Design

This retrospective, observational cohort study was carried out in two operative settings (Diagnostic and Interventional Bronchoscopy Unit -Unit A, and Otolaryngology Unit-Unit B) at the University Hospital of Modena (Italy). These units follow different routinely applied protocols to treat tracheal benign stenosis. Endoscopic treatment through mechanical dilatation via rigid bronchoscopy and subsequent stent placing (ST) is performed in Unit A, whilst balloon dilatation via direct laryngoscopy (BA) is used in Unit B.

Procedures of Unit A have been performed in the operating room with a Dumon rigid bronchoscope (Efer Medical, La Ciotat, Cedex, France) under general anesthesia. A silicone stent (NOVATECH Dumon stents, Boston Medical Products, Inc., Westborough, MA, USA) sized 16-14-16mm for females and 18-16-18 mm for males is placed after mechanical dilatation. Stent was planned to be maintained for 1 year and subsequently removed.

Procedures in Unit B are performed under general anesthesia. The patient's larynx is exposed using a rigid laryngoscope, and endoscopy is undertaken to assess the area of tracheal stenosis. In some circumstance, a long-acting corticosteroid is injected in the submucosa surrounding the stenotic area. Furthermore, CO2 laser (4W in a continuous mode) excision of the scarred surface can be performed if indicated. The stenotic area is then serially dilatated with balloon (CRE^{TM} Balloon dilatation catheters, Boston scientific, USA) sized 14mm for females and 16mm for males. Office based tracheoscopy controls are planned 60 days after the procedure and the intervention is repeated if signs of stenosis are detected or symptoms are reported. If needed, another dilation is performed after further 60 days.

This study was approved by Local Ethics Committee (Prot. AOU 0025966/19) and registered on clinicaltrial.gov (trial registration number: NCT04674995). Consent to publish data was acquired from participants.

Population and measures

We collected clinical, endoscopic and radiological data of patients with benign tracheal stenosis admitted in the two units from November 2012 to November 2017. Inclusion criteria were as follows: age >18 years, no indication for resection-anastomosis surgery, Cotton Myer $\geq$ grade II, available follow-up of at least 3 years after endoscopic surgery, no previous tracheal surgery.

Exclusion criteria were as follows: age > 80, presence of subglottic stenosis, stent intolerance which required removal in the first year after endoscopic approach, performance status > 2, end-stage chronic pulmonary disease, life-threatening stenosis with urgent endoscopic treatments, any neoplastic stenosis of the airways, tracheal benign stenosis caused by excessive dynamic airway collapse [EDAC], tracheobronchomalacia [TBM]).

Chart review, medical record, and archival data analysis were performed at each unit. The following variables were collected in an electronic database: demographic data, Charlson Index for comorbidity assessment, adverse events, need for re-intervention, type, extension and etiology of tracheal stenosis, Cotton Meyer grade at the time of intervention, laser appliance, use of steroids. According to their morphological aspects, stenoses were classified into two groups: simple and complex. Simple stenosis was defined as a lesion of the tracheal wall mucosa without tracheomalacia or cartilaginous involvement, with a longitudinal luminal occlusion < 1 cm. Complex tracheal stenosis was defined as tracheal stricture with longitudinal tracheal involvement > 1 cm, plus various degrees of cartilage involvement, in some cases also associated with malacia.

The etiology of tracheal stenosis was defined based on rheumatologic evaluation, history of intubation/tracheostomy and airway trauma. Patients for whom a full workup was unrevealing for etiology, were categorized as having an idiopathic stenosis.

Patients included in this study were divided into two groups: 1) patients undergoing endoscopic treatment through laryngoscope followed by balloon dilatation (BA), and 2) patients undergoing endoscopic treatment through rigid bronchoscope followed by stent placement (ST).

Outcomes

Our primary purpose was to compare the clinical efficacy of the two therapeutical techniques on tracheal stenosis over time. We considered patients to be “stabilized” (as compared to “not stabilized”) if they did not report any significant respiratory symptoms, or if they need re-intervention, or presented evidence of re-stenosis. This last variable was assessed during an endoscopic examination 2 years after an initial time period of 12 months from the date of the procedure (Figure 1 supplementary materials). The time period elapsed before starting the follow-up was chosen either because: 1) BA required several interventions to achieve an ideal tracheal patency in the year apart, or 2) effectiveness on tracheal patency with the maintenance of the tracheal prosthesis in ST was evaluated over the same period.

The secondary aim of the study was to compare the adverse events rate in the two treatment groups.

All patients were followed with fiberoptic bronchoscopy at 1, 3, 6 and 12 months after initial treatment. The trachea was subsequently endoscopically examined at 1, 6, 24 and 48 months from then. Restenosis was defined as the presence of any type of stenosis associated with recurrent respiratory symptoms or evidence of stenosis > 1 Cotton-Myers grade with or without symptoms.

Statistical Analysis

Sample size calculation was performed assuming an estimated relapse rate of 50% for patients in the BA group [9] with an estimated 20% reduction in ST (explorative analysis in 20 patients). Assuming $\alpha = 0.05$, power 80% and an enrollment ratio of 1:1 (according to the overall number of patients referred at each unit), a sample size of 66 patients was calculated to perform analysis on the primary outcome.

Baseline and clinical characteristics in the BA and ST groups, and in the stabilized and not stabilized categories were compared. Continuous variables were expressed as median and interquartile ranges (IQR) and compared by Mann-Whitney 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.

Time to relapse by groups, starting 12-month after the initial procedures, was compared using unweighted Kaplan-Meier curves and univariable and multivariable Cox regression analysis with baseline fixed covariates. The treatment effect was reported by means of unadjusted and adjusted hazard ratio (HR) with 95%CI. Two key confounders (age and Cotton Meyer grade) were identified 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 the etiology (idiopathic), the type (complex) and the degree of stenosis (>70% of the lumen reduction), we formally included an interaction term in the Cox regression model. Results were then showed after categorizing the population in two strata using categorical separation for dichotomous variables (idiopathic versus non-idiopathic, and complex versus non-complex), and the overall median value for continuous variables (% of lumen occlusion). The impact of BA or ST on pre-specified secondary

outcomes was carried out through Fisher's exact test. A two-sided test of less than 0.05 was considered to be significant.

Statistics was obtained 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

Seven-hundred-sixteen patients diagnosed with tracheal stenosis were referred to units A and B over the considered time period. Out of the total number, 134 (18.7%) presented benign tracheal stenosis with >50% of lumen reduction on the CT scan at the time of diagnosis. Among the 87 eligible patients, 66 were included (see **Figure 1**).

Figure 1

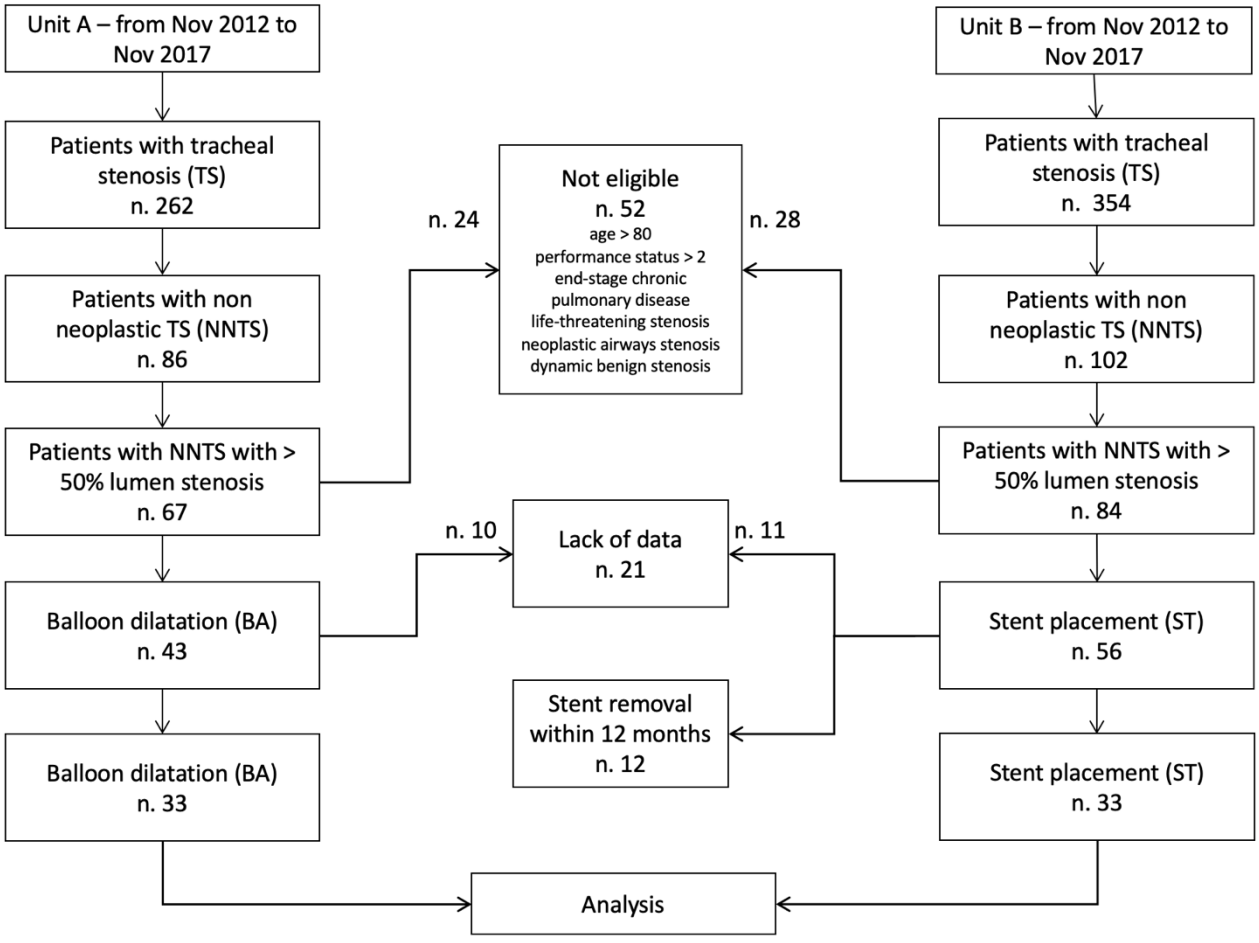

Fig. 1. Study flow-chart.

Table 1 shows the general and clinical characteristics (etiology, type and extension of stenosis) of the population in study. The patients included in the BA group were younger and showed a lower prevalence of Cotton Meyer III grade stenosis than in the ST group, whilst there was no difference in terms of etiology and type of tracheal stenosis. Table 1 shows the same characteristics in the two study groups and according to the pre-defined outcome in the long-term. Within the BA group, the "stabilized" patients (58%) were younger (51 vs 58 years, p=0.002), reported more frequent simple stenosis (53% vs 14%, p=0.03) and a lower number of laser sessions (1 vs 11, p<0.001), and did not present any autoimmune etiology as compared to the "non-stabilized" ones. In the ST group, patients "stabilized" (85%) only reported a lower rate of autoimmune stenosis than in the "not stabilized" category (4% vs 80%, p=0.001). With regard to the complex stenosis, success rate was 71% (20/28), and 47% (9/19) in the ST and BA group respectively (p = 0.01).

Table 1

Variable	Cohort									
	Overall				BA (n=33)			ST (n=33)		
	Total n=66	BA n= 33	ST n=33	p value	Cured n= 19	Not cured n=14	p value	Cured n= 28	Not cured n=5	p value
Age, score (IQR)	68 (52-76)	56 (47-69)	75 (57-80)	0.002	51 (45-63)	58 (55-69)	0.002	75 (57-80)	73 (71-77)	n.s. (0.4)
Male, n (%)	37 (56)	17 (52)	20 (61)	n.s. (0.6)	7 (37)	10 (61)	n.s. (0.1)	18 (64)	2 (40)	n.s. (0.4)
Charlson index, score (IQR)	3 (1-5)	2 (1-4)	3 (1-5)	n.s. (0.2)	1 (1-3)	4 (3-5)	n.s. (0.2)	5 (3-6)	5.5 (5-7)	n.s (0.4)
Type of stenosis										
Simple, n (%)	20 (30)	12 (36)	8 (24)	n.s (0.4)	10 (53)	2 (14)	0.03	8 (29)	0 (0)	n.s (0.3)
Complex, n (%)	46 (70)	21 (64)	25 (76)	n.s. (0.4)	9 (47)	12 (86)	0.03	20 (71)	5 (100)	n.s (0.3)

Degree of stenosis, % (IQR)	70 (50-80)	67 (50-79)	73 (60-85)	n.s. (0.1)	64 (50-76)	70 (55-78)	n.s. (0.1)	75 (55-80)	60 (50-73)	n.s. (0.6)
Cotton Meyer grade										
Grade II, n (%)	27 (40)	18 (55)	9 (27)	0.04	12 (63)	6 (43)	n.s. (0.3)	8 (29)	1 (20)	n.s. (0.9)
Grade III, n (%)	39 (60)	15 (45)	24 (73)	0.04	7 (37)	8 (67)	n.s. (0.3)	20 (71)	4 (80)	n.s. (0.9)
Etiology										
Idiopathic, n (%)	31 (47)	15 (45)	16 (49)	n.s. (0.8)	10 (53)	5 (36)	n.s. (0.5)	15 (54)	1 (20)	n.s. (0.3)
Autoimmune, n (%)	10 (15)	5 (15)	5 (15)	n.s. (0.9)	0 (0)	5 (36)	0.01	1 (4)	4 (80)	0.001
Iatrogenic, n (%)	25 (38)	13 (39)	12 (36)	n.s. (0.8)	9 (47)	4 (29)	n.s. (0.3)	12 (43)	0 (0)	n.s. (0.2)
Laser treatment, n (%)	12 (18)	12 (36)	---	---	1 (8)	11 (55)	<0.001	---	---	---
Steroid treatment, n (%)	14 (21)	14 (42)	---	---	6 (32)	8 (57)	n.s. (02)	---	---	---

Table 1. Demographic and clinical characteristics of the 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

Outcomes

On the long-term follow-up (2-year), unadjusted Kaplan-Meier estimates showed the beneficial effect of ST compared to BA on tracheal stenosis (HR=3.9 95%CI [1.5-9.8], p=0.01) (Figure 2, panel A). Moreover, the same beneficial effect following ST was found when referring to the stratified analysis (Figure 2, panel B-D) according to either etiology (idiopathic or non-idiopathic), type (complex or non-complex) and degree of stenosis (>70% or < 70%).

Figure 2

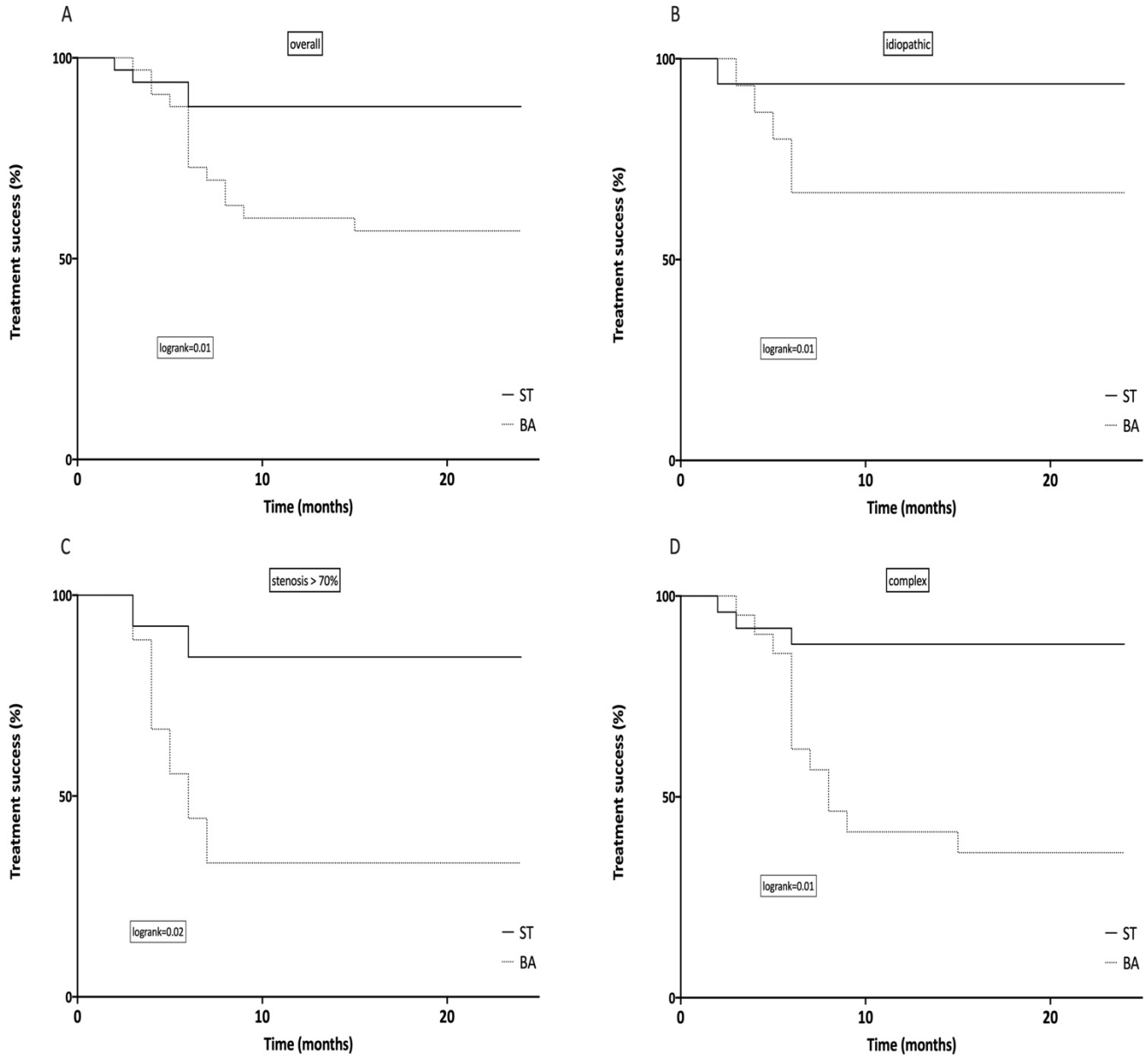

Fig. 2. Kaplan-Mayer curves showing treatment efficacy by groups in the long-term (2 years), in the whole population (panel A), in patients with idiopathic stenosis (panel B), in patients with complex stenosis (panel C), and in patients with degree of tracheal stenosis > 70% (panel D).

After controlling for the key identified confounders (see Methods), results were almost superimposable, whereas stratified analyses showed that difference varied by etiology, type and degree of stenosis (**Table 2**).

Table 2.

Unadjusted and adjusted relative hazards of 24 months treatment success

	Unadjusted HR (95%CI)	p value	Adjusted* HR (95%CI)	p value
		All cases		
Balloon dilatation	1		1	
Stent placement	3.9 (1.5-9.8)	0.01	3.6 (1.2-10)	0.01
		Stratum etiology idiopathic		
Balloon dilatation	1		1	
Stent placement	4.6 (1.2-21)	0.03	3.9 (1.1-24)	0.04
		Stratum etiology non idiopathic		
Balloon dilatation	1		1	
Stent placement	2.1 (0.7-6.4)	0.1	1.7 (0.5-8)	0.2
		Stratum complex		
Balloon dilatation	1		1	
Stent placement	6 (2.3-17)	0.002	4.2 (1.9-11)	0.01
		Stratum noncomplex		
Balloon dilatation	1		1	
Stent placement	1.2 (0.3-12)	0.7	1.1 (0.2-10)	0.8
		Stratum stenosis > 70%		
Balloon dilatation	1		1	
Stent placement	5.5 (1.3-23.7)	0.01	4.4 (1.2-19.2)	0.03
		Stratum stenosis < 70%		
Balloon dilatation	1		1	
Stent placement	3.3 (1.4-9.2)	0.01	2.9 (1.2-8.6)	0.02

Table 2. Overall and stratified treatment efficacy

Adjusted and unadjusted hazard ratios from fitting a standard Cox regression model. Data are presented for the overall population and after stratification for etiology, type and extension of the stenosis.

*Adjusted for age and Cotton Meyer grade

Finally, BA showed a statistically significant (p=0.01) lower rate of adverse events (**Table 3**).

Table 3.

Adverse event	Cohort			p value
	Total n=66	Balloon dilatation n=33	Stent dilatation n=33	
Secretions, n (%)	4 (6)	2 (6)	2 (6)	
Granulomas formation, n (%)	6 (9)	2 (6)	4 (12)	
Patient intolerance, n (%)	4 (6)	----	4 (12)	
Stent migration, n (%)	1 (2)	----	1 (3)	
Stent occlusion, n (%)	1 (2)	----	1 (3)	
Tracheal edema/malacia, n (%)	2 (3)	----	2 (6)	
Total, n (%)	18 (27)	4 (12)	14 (42)	0.01

Table 3. Adverse event reported in the general population and on the basis of treatment. The data are presented as a numerical and percentage value. The statistical significance was set for $p<0.05$.

Discussion

This study shows that stent placement (ST) and subsequent removal (1 year later) has a better effect on long-term (2-year) stabilization of tracheal patency after endoscopic treatment for benign tracheal stenosis than balloon dilation (BA) technique. The different success rate between the two endoscopic treatments is significant in patients with idiopathic etiology, complex stenosis, a tracheal lumen >70%. Notwithstanding, ST is burdened with a significant rate increase of side effects compared with BA. Finally, we have shown that the use of laser in the BA group and autoimmune stenosis, are both associated with a risk of endoscopic treatment failure.

Actually, there is no definitive consensus on the endoscopic management of tracheal stenosis not eligible for surgery. Significant concerns about stent placement are patient tolerance and the risk of increasing the length of tracheal stenosis, which may complicate any future surgical approach to cure [10] . Despite this, previous studies reported that only simple web-like stenosis can be treated endoscopically using mechanical dilatation, with a success rate ranging from 60 to 95%, whilst complex stenosis with cartilaginous involvement are more likely to obtain effective stabilization of tracheal lumen by stenting [11–14]. In our study, success rate to treat simple stenosis did not show any difference between BA and ST group, thus suggesting that tracheal dilation without prosthetic implantation should be the treatment of choice with this type of stenosis. Conversely, a very high relapse rate (>90% of cases) has been reported in complex tracheal stenosis treated with BA only, therefore indicating that stent placement may be the best solution in most of these cases [15] .

Brichet et al. reported a low success rate (17.6%) in the management of complex stenosis with stent placement, however endoprostheses were left in place for only 6 months [16] at difference with our study. More recently, Galluccio et al. treated 33 patients with complex stenosis with BA+ST and reported 69% success rate; however, mean duration of stenting (18 months) was longer [11]. A similar success rate in similar patients was also reported in the study by Dalar L et al, with a mean duration of stenting time of 11.9 month [13].

Timing of stent removal seems to be crucial for endoscopic treatment success in the long-term; indeed, a stented tracheal stenosis can progressively mature and stiffen over a longer time, thus resulting in definitive stabilization of patency. In an earlier study, tracheal stent has been removed after 18 months, and 17 out of 21 patients did not show any relapse of stenosis 259 days later [17].

In our study, patient selection and timing of stent removal could have contributed to the high success rate in the treatment of complex stenosis in ST group. Notably, the exclusion of patients who required stent removal due to intolerance in the 12 months following endoscopic treatment certainly have influenced the study primary outcome among ST patients. However, data available in literature and clinical experience suggest that the long-term efficacy with stent placement can only be achieved when the prosthesis has remained in place for the necessary time (i.e., > 1 year) to stabilize trachea.

Notwithstanding the positive results with ST strategy, adverse events were reported to be higher than with BA. Indeed, stent-related complications are the greatest concern associated with ST, and could lead to further bronchoscopic treatment. The main adverse events reported in previous studies are: mucostasis (30%-50% of cases), stent migration (5-41%), and development of tissue granulation (19-33%) [18–20]. The incidence of adverse events in our study was lower than in previous series. It is likely that selection of patients, excluding those with severe respiratory comorbidities and low performance status, might have contributed to this result. However, 2 patients in ST group (6%) showed edema and tracheomalacia once the stent was removed, then required a second tracheal stenting. This adverse event highlighted the importance of evaluating inflammatory state and location stenosis at the tracheal level, to prevent/avoid stent-related risk of major complications. In particular, much more attention is needed in proximal tracheal stenosis, close to the cricoid ring in the subglottic area. Indeed, the wall of the subglottic region presents with a layer of loose subepithelial connective tissue containing a dense capillary plexus supplied by the cricothyroid branch of the superior thyroidal artery [21]. This capillary plexus is particularly enhanced in acute stenosing laryngotracheobronchitis of children (pseudocroup) and in adult local vasculitis (i.e., granulomatosis with polyangiitis), both conditions presenting with edema and airway stenosis. Stent placement in this area could result in inflammation, vessels' enlargement, and increased blood flow, which may lead to edema and obstruction. Furthermore, studies in animal models have shown that a systemic inflammatory response with increased IL-8 expression in blood may occur after stent implantation, suggesting that stent-related radial and shear stress forces of the tracheal wall could have significant influence on the systemic inflammation, especially when mucosal inflammation is endoscopically evident [22].

Another goal of our study was to demonstrate the cause-effect relation between etiology of stenosis and the outcome of endoscopic treatment. Indeed, curability rate is significantly higher in

ST group than in BA only in patients with idiopathic stenosis (Table 2). This condition is a rare fibrotic disease of unclear etiology that almost exclusively affects women, and mainly involves the subglottic area bounded inferiorly by the first two tracheal rings [23]. Autoimmune tracheal stenosis led to a lower probability to be successfully treated in both groups, suggesting that this type of lesion has a high relapse rate regardless of the endoscopic technique used, and may constitute one of the main issues in tracheal diseases. Tracheostomy as a late outcome due to treatment failure is more prevalent in autoimmune tracheal injury and in patients with tracheomalacia [24].

Last, data resulting from the present study also showed that laser technique was less used in successfully treated patients of BA group than in ST, suggesting that in patients undergoing endoscopic dilatation the subsequent use of laser to obtain the excision of the scar area may be associated with relapse of stenosis. Lasers are often used in the treatment of pathogenic airway process, although several reports have described the occurrence of late tracheal stenosis [25,26]. In animal model, laryngotracheal laser-induced injury was due to mucosal and vascular changes which persist chronically, with an extensive re-organization of the connective tissue and the underlying cartilage [27]. Despite these observations, previous retrospective studies have not reported worse outcomes in patients undergoing endoscopic laser surgery compared to those who did not [28]. Taking as a whole the results that we observed comparing BA and ST modalities, we would suggest the following treatment approach in patients with benign tracheal stenosis without indication for open surgery.

Simple stenosis should be dilatated, and scar cutting may be performed with cold knife avoiding laser, while stent positioning is advisable only in case of relapses. Moreover, in patients with complex tracheal stenosis, the endoscopic therapy should be based on a multidisciplinary discussion considering the anatomical location of stenosis, the inflammatory state of the laryngeal-tracheal mucosa and the level of cartilage injury.

In patients with subglottic stenosis on the cricoid or supra-cricoid area, or with a stenosis showing signs of mucosal inflammation, dilation should be the first option for endoscopic treatment. Moreover, in complex tracheal stenosis with involvement of the sub-cricoid area (first-second tracheal ring), stent placement should be preferred first. However, tracheal stenting could also be considered in case of frequent relapse after dilation.

Although present findings are intriguing, limitations to be emphasized still remain. First and most important, the retrospective design of the study and the limited sample size cannot lead us to draw

a definitive conclusion. It is worth noticing that the allocation of patients to receive care by otolaryngology or interventional pulmonology was based on organizational reasons and was not related to the severity or type of stenosis. Second, enrollment criteria might have influenced the results between groups. In this line it should be noticed that patients in the ST group resulted significantly older as compared to BA. Third, for patients that had undergone stent placement, we decided to measure complications only after the first 12 months excluding those needing early stent removal for intolerance, in order to assess the real effectiveness of the technique that requires a sufficient amount of time to achieve tracheal stabilization. Furthermore, we have used the Myer Cotton scale to assess the grade of tracheal stenosis, although it is more suitable for subglottic stenosis. Moreover, we acknowledge that treating simple stenosis with tracheal stenting might not be recommended as initial approach. However, the high rate of recurrence [13] and the need to further several re-interventions may have justified this strategy. We decided to include these cases in our retrospective analysis to generate reliable data regarding treatment success rate and adverse events between stenting and balloon dilatation technique also in this subset of stenosis. We believe that present study may help to open discussion in clarifying the role and the risk-benefit profile of different endoscopic therapies for benign tracheal stenosis for open surgery. Also, this may warrant future prospective studies to confirm data.

Conclusion

This retrospective study suggests that ST placement and subsequent removal after 1 year seems to be more effective in achieving stabilization on tracheal patency in complex benign tracheal stenosis compared to BA technique. However, ST is burdened with a significantly higher number of adverse effects compared to BA, that limit widespread use of this technique. In non-operable complex stenosis, multidisciplinary evaluation with assessment of localization, inflammatory state of the mucosa and cartilage involvement of stenosis, is necessary to choose the first endoscopic approach technique with the best risk-benefit profile.

Appendix – Supplementary materials

Figure S1

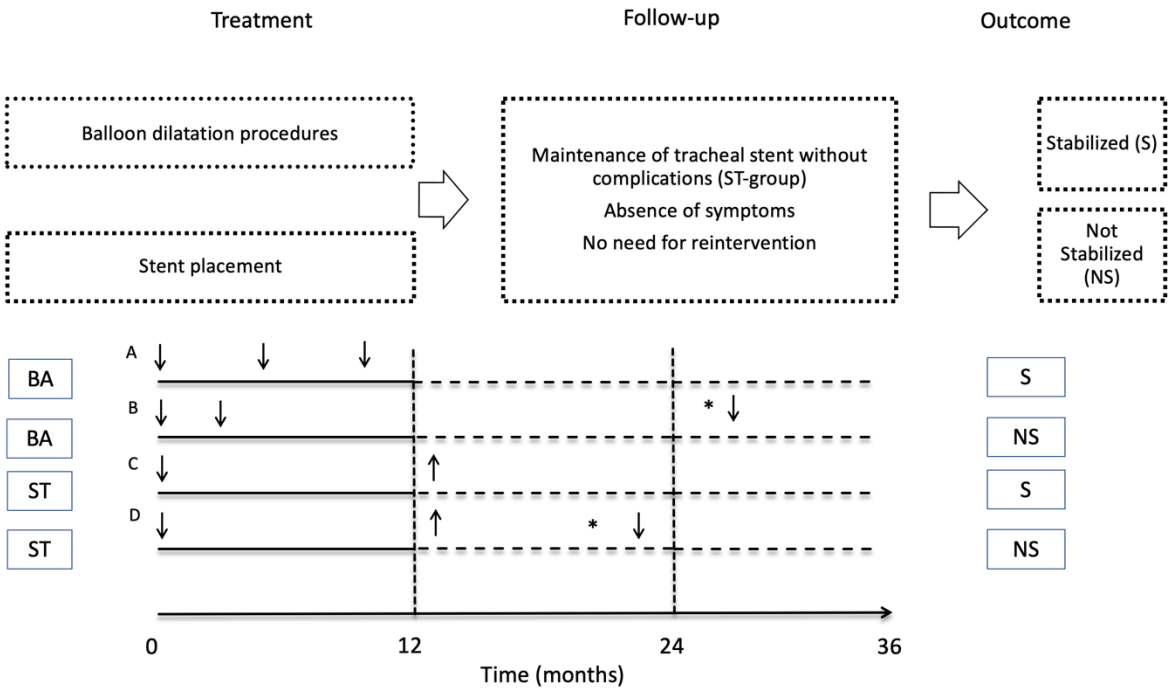

Figure S1. Study design and follow-up period with definition of the primary outcome. (↓) Indicates endoscopic procedure. (*) Indicates symptoms relapse. (↑) Indicate stent removal. Patients A and C were classified as "stabilized", whereas patients B and D were classified as "not stabilized" (for details see text in the Methods section).

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Chapter 3

Risk factors for distal metastasis and clinical prognosis of patients with sovra-glottic airways cancer non-metastatic at diagnosis: a retrospective study

Abstract

Background. Distant metastasis (DM) development in Oropharyngeal Squamous Cell Carcinoma (OPSCC) represents an important prognostic factor. The identification of a phenotype of metastatic patients may better define therapeutic and follow-up programs.

Methods. We included 408 patients with OPSCC, non-metastatic at the time of diagnosis, and treated with curative intent. The Overall Survival (OS) analyses were performed and the impact of developing DM on survival was analyzed through Cox proportional-hazard regression model.

Results. 57 (14%) patients develop DM. 302 (74%) were p16+ OPSCC and 35 of them experienced DM. Advanced clinical stage, smoking, p16-status, response to primary treatment, and loco-regional relapse influence the DM rate. Only in the p16+ group, DM onset results in a greater impact on OS (p<0.0001). Lung metastases have a better OS compared to non-pulmonary ones (p=0.049).

Conclusion. This retrospective study shows a possible stratification of OPSCC patients based on the risk of the development of DMs.

Introduction

During the last few decades, the epidemiology of Oropharyngeal Squamous Cell Carcinoma (OPSCC) has changed due to the decline in smoking and alcohol consumption and the increasing number of lifetime oral sex partners. Human Papilloma Virus (HPV) infection was found to play an important role in OPSCC pathogenesis, especially virus genotype 16, 18, 33, 35[1–3]. Tumor HPV status was also identified as a strong and independent biomarker of prognosis: patients with HPV-negative (HPV-) OPSCC have a higher risk of distant metastases (DMs) compared to HPV-positive (HPV+) ones[4,5]. Moreover, different outcomes have been observed after distant progression: patients with p16+ OPSCC have significantly better Overall Survival (OS) after DM than p16- ones, either in case of locoregional failure, salvage surgery, and no salvage surgery[6]. Due to these different outcomes and biological behavior, the most recent edition of the American Joint Committee on Cancer (AJCC) staging system defined p16+ and p16- OPSCCs as separate entities[7–9]. For this aim, the College of American Pathologists recommends the p16 immunohistochemistry testing or other HPV-specific tests in all the patients affected by OPSCC[10].

Despite better loco-regional control and survival, 10% to 25% of patients with p16+ OPSCC experience disease metastatization within 3 years of completing primary therapy[4,11–14]. Moreover, the DM rate remains unchanged in p16+ patients compared to p16- ones[4,11,15]. Unlike p16- patients, in which loco-regional failure predominates, DMs represent the major reason for primary treatment failure in p16+ patients[11,15]. The time of development of DM is different: some Authors have observed that p16+ DMs occur significantly later than in patients with p16- disease[11,16]. Additionally, it seems that p16+ OPSCCs are characterized by a "disseminating phenotype"[11]: DMs have a propensity to involve unusual and a greater number of subsites compared with p16- tumors[16,17]. Although the lung is still the most common site of DMs, in p16+ OPSCC metastases have been reported also to bone and liver[6], skin, brain[18], kidney, muscle[11,16], and non-regional lymph node[15].

Aim of this study is to identify patients and tumor-related characteristics capable of predicting the risk of developing DM in the OPSCCs' cohort and to define the oncological outcomes of two groups of patients (p16+ vs p16-) that developed DM after curative treatment with a 5-year follow-up. To better understand the burden of DM development we also calculated OS from the diagnosis time of DM. Furthermore, we have analyzed oncological outcomes by comparing pulmonary and non-

pulmonary DM and the impact of local regional relapse (LRr) on OS in DM and non-metastatic (NDM) groups correlating with the HPV status.

MATERIAL AND METHODS

Study design

This is a retrospective monocentric study performed in a tertiary academic center at the Bronchoscopy Unit and the Otorhinolaryngology Unit of the University Hospital of Modena. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee (CE AVEN Emilia-Romagna: 0018649/22). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Study population

We included patients with OPSCC who were treated with curative intent at the University Hospital of Modena (Italy), after a clinical evaluation at the Head and Neck Multidisciplinary Tumor Board (MTB), between January 2009 and December 2019.

Inclusion criteria were as follows: diagnosis of OPSCC with no evidence of metastatic involvement at the time of diagnosis addressed to any of the following treatments with curative intent: surgery, endoscopic treatment, radiotherapy, and chemoradiotherapy.

The exclusion criteria were lack of core demographic or clinical data at medical record analysis, follow-up not available or shorter than 3 years, patients who experience synchronous or metachronous head and neck malignancies, and/or who were already treated with chemoradiation therapy.

Data collection

We retrieved patients' information from the analysis of medical records and the Modena MTB database.

Among the collected data, we focused on demographics, HPV status (defined as positive p16 staining on histological specimen), clinical staging at diagnosis (according to AJCC 8th Edition)[19], and the type of treatment performed.

Outcomes

Primary outcomes were: i) risk factors in DM development; ii) comparison of OS, between DM and NMD-group related to p16-status calculated from the diagnosis of the primary and the time of DM development.

Secondary outcomes: comparison of OS between pulmonary DM and non-pulmonary DM, the impact of LRr on OS in DM and NDM-group correlating with the HPV-status.

Statistical Analysis

A priori sample size calculation on the primary outcome was based on available data on 5-year survival rates among patients with oropharyngeal cancer with and without DM at the time of diagnosis (https://www.cancer.net/cancer-types/oral-and-oropharyngeal-cancer/statistics). Assuming α=0.05 and power of 85%, a sample of 51 patients per group (total study population of 102 patients) was sufficient to give value to the primary outcome.

Demographic and clinical variables were compared between those who developed DM and those who did not (NDM cohort); t-test and Wilcoxon-Mann-Whitney test served for continuous variables, whereas categorical variables were compared by $\chi 2$ test or Fisher's exact test, as appropriate. The association between demographic and clinical characteristics with the onset of DM was tested using univariable and multivariable logistic regression model. The OS analysis was performed with participants' follow-up accrued from the date of diagnosis until death. Time to death was compared using unweighted Kaplan-Meier curves and the impact of developing DM on survival was analyzed through unadjusted and adjusted Cox proportional hazard regression model. To test the hypothesis that the difference between groups might vary according to p16-status, we formally included an interaction term in the COX regression analysis. Results were further presented after categorizing the population into two strata using categorical separation and showed using unweighted Kaplan-Meier curves. In a post-hoc sensitivity analysis, OS was assessed for DM cohort according to the site of metastasis using unweighted Kaplan-Meier curves.

In another sensitivity analysis unweighted Kaplan-Meier curves were used to assess the OS according to p16-status. Further, the time to the development of DM was compared between p16+ and p16- using unweighted Kaplan-Meier curves and analyzed through a cumulative incidence function model using Fine-Grey competing risk model and considering mortality as competing risk.

Moreover, the effect of the combination of p16-status and the onset of local relapse on OS was further explored through unweighted Kaplan-Meier curves according to the development of DM. Finally, an OS analysis was performed for DM patients with participants' follow-up accrued from the date of DM onset until death according to the p16-status and the site of metastatic involvement. Missing data were not imputed. Significance was set for p-values <0.05. Statistics were performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Study population

A total of 442 patients with OPSCC were referred to our institution between January 2009 and December 2019. Among them, 408 resulted eligible according to the inclusion criteria (**eFigure 1, Supplementary Material)**. Of these, 312 were males (76%) and 96 females (24%), with a median age at diagnosis of 63 (interquartile range [IQR] 55-70) years.

Table 1.

Variable	Overall n=408 (100)	No distant metastasis (NDM) n= 351 (86)	Distant metastasis (DM) n = 57 (14)	p value
Age at diagnosis, years (IQR)	63 (55 – 70)	63 (55 – 70)	63 (55 – 71)	0.7
Male sex, n (%)	312 (76)	268 (76)	44 (77)	0.5
Smoker status				
Never, n (%)	**108 (26)**	**99 (28)**	**9 (16)**	**0.05**
Former, n (%)	130 (32)	106 (30)	24 (42)	0.1
Active, n (%)	170 (42)	146 (42)	24 (42)	0.9
Site				
Occult, n (%)	1 (0.2)	1 (0.3)	0 (0)	0.9
Base of the tongue, n (%)	155 (38)	128 (36)	27 (47)	0.1
Tonsil, n (%)	224 (55)	199 (57)	25 (44)	0.1
Soft palate, n (%)	25 (6)	22 (6)	3 (5)	0.9
Posterior wall, n (%)	**3 (1)**	**1 (0.3)**	**2 (4)**	**0.05**
Grading,				
Gx, n (%)	127 (31)	112 (32)	15 (26)	0.4
G1, n (%)	4 (1)	4 (1)	0 (0)	0.9
G2, n (%)	62 (15)	55 (16)	7 (12)	0.7
G3, n (%)	215 (53)	180 (51)	36 (61)	0.1
HPV p16 +, n (%)	**302 (74)**	**267 (76)**	**35 (61)**	**0.02**
HPV p16 -, n (%)	**106 (26)**	**84 (24)**	**22 (30)**	**0.02**
cT	*n=407*	*n=351*	*n=56*	
cT0 o cTis, n (%)	5 (1)	5 (1)	0 (0)	0.9
cT1, n (%)	**80 (20)**	**75 (21)**	**5 (9)**	**0.03**
cT2, n (%)	**101 (25)**	**93 (26)**	**8 (14)**	**0.05**
cT3, n (%)	33 (8)	25 (7)	8 (14)	0.1
cT4a/cT4, n (%)	**179 (44)**	**146 (42)**	**33 (59)**	**0.03**
cT4b, n (%)	9 (2)	7 (2)	2 (4)	0.4

cN p16 +	*n=288*	*n=255*	*n=33*	
N0, n (%)	51 (18)	46 (18)	5 (15)	0.8
N1, n (%)	129 (45)	117 (46)	12 (36)	0.4
N2, n (%)	103 (36)	87 (34)	16 (48)	0.1
N3, n (%)	5 (2)	5 (2)	0 (0)	0.4
cN p16 -	*n=89*	*n=71*	*n=18*	
N0, n (%)	23 (26)	20 (28)	3 (17)	0.4
N1, n (%)	15 (17)	13 (18)	2 (11)	0.7
N2a, n (%)	3 (3)	2 (3)	1 (6)	0.5
N2b, n (%)	28 (31)	24 (34)	4 (22)	0.4
N2c, n (%)	**17 (19)**	**10 (14)**	**7 (39)**	**0.04**
N3a, n (%)	2 (2)	2 (3)	0 (0)	0.9
N3b, n (%)	1 (1)	0 (0)	1 (0)	0.9
Treatment				
Surgery, n (%)	33 (8)	32 (9)	1 (2)	0.07
Radiotherapy (RT), n (%)	78 (19)	67 (19)	11 (19)	0.9
Chemo-radiotherapy (CTRT), n (%)	215 (53)	180 (51)	35 (61)	0.2
Surgery + RT, n (%)	33 (8)	27 (8)	6 (11)	0.4
Surgery + CTRT, n (%)	44 (11)	40 (11)	3 (7)	0.2
None	5 (1)	5 (1)	0 (0)	0.8
Response, n (%), *n=363*	**305 (84)**	**267 (87)**	**38 (68)**	**0.003**
Loco-regional relapse, n (%), *n=318*	**71 (22)**	**46 (17)**	**25 (53)**	**<0.0001**

Table 1. General and clinical features of the study population presented as a whole and according to the development of distant metastasis. Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.

Abbreviations *IQR = Inter Quartile Range; HPV = Human Papilloma Virus; RT = Radiotherapy; CTRT = Chemoradiotherapy*

Table 1 displays the demographic and clinical features of the population according to the development of DM. We found that 108 (26%) patients had never smoked and 99 of them did not develop DM. The most frequent subsite of the primary tumor was the tonsil (n=224, 55%), followed by the base of the tongue (n=155, 38%), the soft palate (n=25, 6%), the posterior wall (n=3, 1%). Most of the study population (n=302, 74%) showed positiveness for p16. The most represented clinical stage was the cT4/cT4a with a total of 179 (44%) patients (146 among the NDM group and 33 among the DM group). In the NDM-group, 93 (26%) patients were cT2 at the diagnosis, while

75 (21%) patients were cT1. In the DM group, 16 (28%) patients were cT2 and cT3, while 5 (9%) were cT1. For p16+ patients, cN2 (n=16, 48%) resulted the most frequent N involvement among those who developed DM, followed by cN1 (n=12, 36%). In the p16- cohort, the most common clinical N-stage was cN2b (n=28, 31%), while cN2c was more frequently observed in those who developed DM (n=7, 39%). Overall, exclusive radiotherapy or chemo-radiation treatment were the most performed therapies (n=293, 72%), even in those who further developed DM (n=46, 80%). After primary treatment, a complete response was observed in 305 (84%) patients (38 [12%] in those who develop DM). Moreover, 71 (22%) patients experienced an LRr (25 (53%) of those with further onset of DM).

Risk factors for DM development

Table 2

		Univariable			***Multivariable***	
Parameter	***OR***	***95% Confidence Interval***	**p value**	***OR***	***95% Confidence Interval***	**p value**
Age at diagnosis	1	0.7 – 1.3	0.9			
Male sex	1.3	0.6 – 2.6	0.5			
Smoker status						
Never	**0.5**	**0.2 – 1**	**0.05**	**0.4**	**0.2 – 0.9**	**0.04**
Former	1.7	0.9 – 3	0.1			
Active	1	0.6 – 1.8	0.9			
Site						
Occult	1	0.7 – 1.9	0.9			
Base of the tongue	1.6	0.9 – 2.7	0.1			
Tonsil	0.6	0.3 – 1.1	0.1			
Soft palate	0.8	0.3 – 2.6	0.9			
Posterior wall	**12.7**	**1.4 - 185**	**0.05**			
Grading						
Gx	0.8	0.4 – 1.4	0.4			
G1	0.7	0.6 – 2	0.9			
G2	0.7	0.3 – 1.7	0.7			
G3	1.7	0.9 – 2.9	0.1			
HPV, p16+	**0.5**	**0.3 – 0.9**	**0.02**	**0.7**	**0.2 – 0.9**	**0.04**
cT						
cT0/cTis	1	0.8 – 1.2	0.9			
cT1	**0.4**	**0.1 – 0.9**	**0.03**			
cT2	**0.5**	**0.2 – 1**	**0.05**			
cT3	2.1	0.9 – 4.9	0.1			

cT4a/cT4	**1.9**	**1.1 – 3.4**	**0.03**	**1.5**	**1.2 – 3**	**0.04**
cT4b	1.8	0.4 – 8.3	0.4			
cN HPV+, p16+						
N0	0.8	0.3 – 2.1	0.8			
N1	0.7	0.3 – 1.5	0.4			
N2	1.8	0.9 – 3.7	0.1			
N3	0.6	0.4 – 8.3	0.4			
cN HPV-, p16-						
N0	0.5	0.1 – 1.8	0.4			
N1	0.6	0.1 – 2.3	0.7			
N2a	2	0.1 – 18	0.5			
N2b	0.6	0.2 – 1.7	0.4			
N2c	**3.9**	**1.2 – 11**	**0.04**			
N3a	0.7	0.1 – 4.6	0.9			
N3b	1.2	0.5 – 2.3	0.9			
Treatment						
Surgery	0.2	0.02 – 1.1	0.7			
RT	1	0.8 – 1.2	0.9			
CTRT	1.5	0.8 – 2.6	0.2			
Surgery + RT	1.4	0.6 – 3.5	0.4			
Surgery + CTRT	0.4	0.2 – 1.3	0.2			
None	0.9	0.4 – 2.4	0.8			
Response	**0.3**	**0.2 – 0.6**	**0.03**	**0.4**	**0.1 – 0.7**	**0.04**
Loco-regional relapse	**5.6**	**2.8 – 10.4**	**<0.001**	**4.5**	**1.7 – 9.4**	**<0.001**

Table 2. Raw and independent association between demographic and clinical features and the development of metastasis. Association is shown through odds ratio (OR) and 95%CI.

IQR = Inter Quartile Range; HPV = Human Papilloma Virus; RT = Radiotherapy; CTRT = Chemoradiotherapy

Table 2 reports the association between demographic and clinical features and the development of DM. A non-smoking status and the presence of p16+ resulted independently and negatively associated with the development of DM (OR=0.4 95% CI [0.2–0.9], p=0.04 and OR=0.7 95% CI [0.2 – 0.9], p=0.04, respectively). Advanced cT-stages (cT4a/cT4) were significantly associated with DM development (OR=1.5 95% CI [1.2-3], p=0.04). For p16- patients, the cN2c resulted in a higher probability of DM onset (OR=3.9 95% CI [1.2–11], p=0.04), although statistical significance was not reached in the multivariable analysis. A complete response to primary treatment was associated with a lower probability of developing DM (OR=0.4 95% CI [0.1–0.7], p=0.04). Conversely, the occurrence of an LRr was associated with DM onset (OR=4.5 95% CI [1.7–9.4], p<0.001).

Survival analyses

The median follow-up time after diagnosis was 56.3 (24.8–74.1) months. Patients who developed DM were at higher risk for dying at 5 years, even after adjusting for potential confounders (adjusted HR=3.2, 95% CI [2.1–4.3], p<0.0001, **Table 3**). The 5-year probability of survival is shown by Kaplan-Meier curves in **eFigure 2** (**Supplementary Material**). The estimated median OS after diagnosis was 34 (16–65) months for those who developed DM and 83 (40–137) months for those who did not (p<0.0001). The estimated 5-year OS after diagnosis was 36.8% (95% CI [24.5–39.1]) for those who developed DM and 76.4% (95% CI [70.3–82.2]) for those who did not.

Table 3

	Unadjusted HR (95%CI)	**p value**	**Adjusted* HR (95%CI)**	**p value**
		All cases		
NDM	1		1	
DM	3.4 (2.2 – 4.9)	<0.0001	3.2 (2.1 – 4.3)	<0.0001
		Stratum p16 -		
NDM	1		1	
DM	1.5 (0.7 – 3.1)	0.26	1.3 (0.5 – 2.8)	0.38
		Stratum p16 +		
NDM	1		1	
DM	4.9 (2.9 – 7.7)	<0.0001	4.8 (2.9 – 7.5)	<0.0001

Table 3. Unadjusted and adjusted relative hazards of 60 months survival. Hazard ratios from fitting a standard Cox regression model

*Adjusted for age at diagnosis, male sex and smoking status

After stratification for p16-status, the onset of DM resulted in a significantly higher risk for 5-year mortality only for those who had p16+ (HR=4.8 95% CI [2.9–7.5], p<0.0001, **Table 3**). The impact of DM development on 5-year OS according to p16 stratification is shown in **Figure 1**, **panel A** for p16+ and **panel B** for p16-. Among p16+ patients, the estimated median OS after diagnosis was 31 (15–52) months for those who developed DM and 86.5 (44.3–138) months for those who did not (p<0.0001), while the OS rate was 24.9% (95% CI [9.7–37.6]) and 79.9% (95% CI [74.6–84.5]), respectively. For p16- patients, the estimated median OS after diagnosis was 47.5 (19.3–92.5) months for those who developed DM and 74.5 (33.2–120) months for those who did not (p=0.3), while the OS rate was 54.5% (95% CI [36.4–77.5]) and 68.1% (95% CI [59.1–79.3]), respectively.

Figure 1

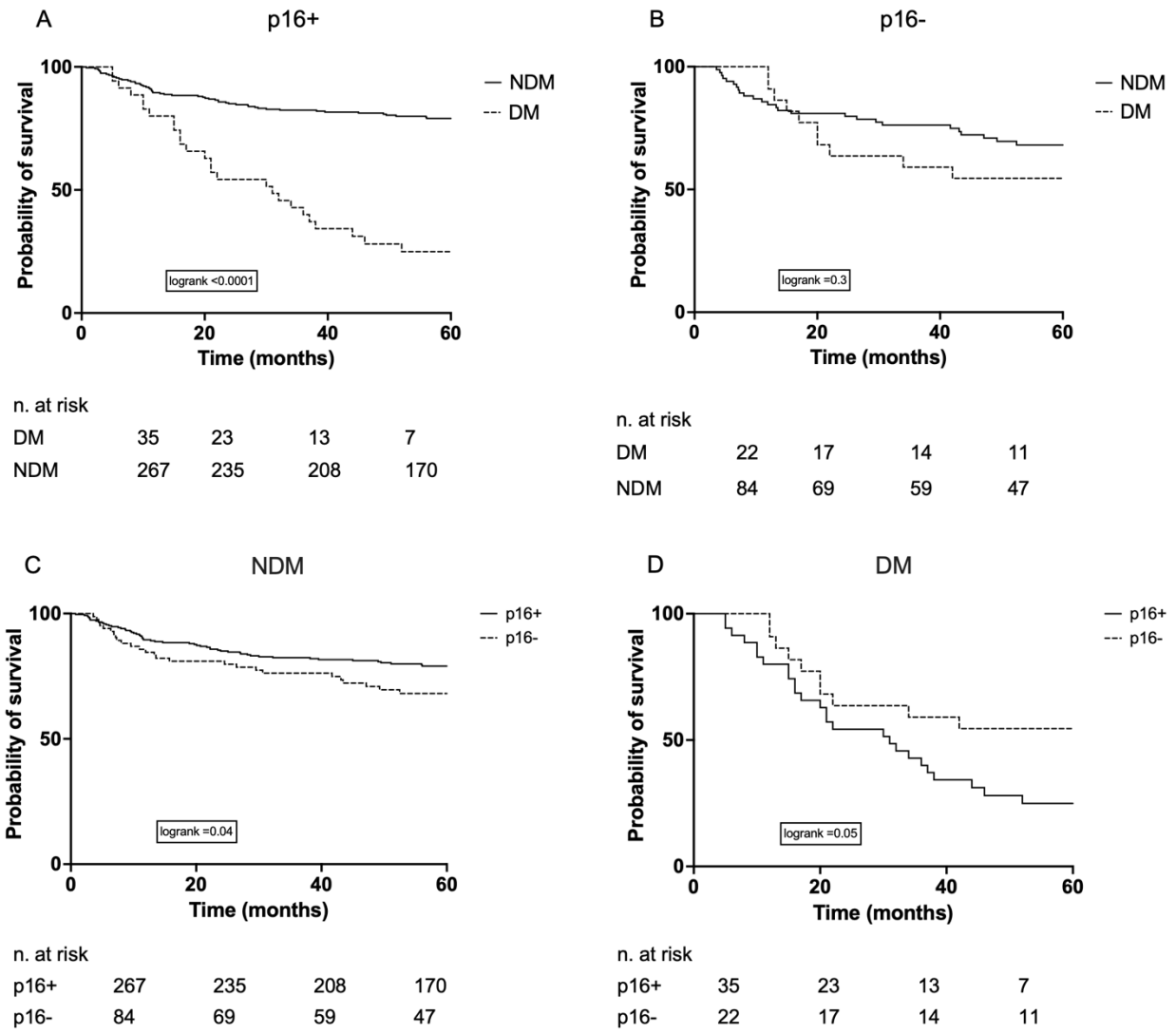
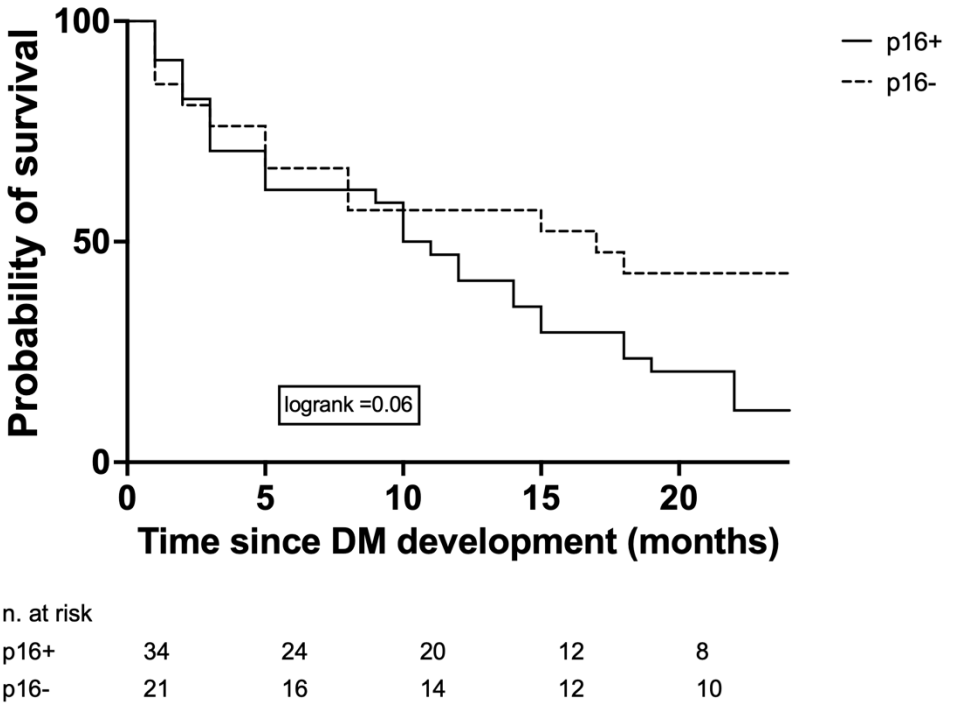


Figure 1. Panels A-B, OS between DM and NDM groups according to p16 status. Panels C-D, OS between p16- and p16+ groups according to the presence or not of DM.

OS = Overall Survival; DM = Distant Metastasis.

For patients who did not develop DM, the presence of p16+ resulted in an improved 5-year OS (p=0.04, **Figure 1**, **panel C**). Conversely, p16+ patients displayed a trend towards a lower 5-year OS, when experiencing the onset of DM (p=0.05, **Figure 1**, **panel D).** The Kaplan-Meier analysis exploring the 2-years OS after distant progression according to p16-status confirmed this trend (**Figure 2)**.

Figure 2.



n. at risk					
p16+	34	24	20	12	8
p16-	21	16	14	12	10

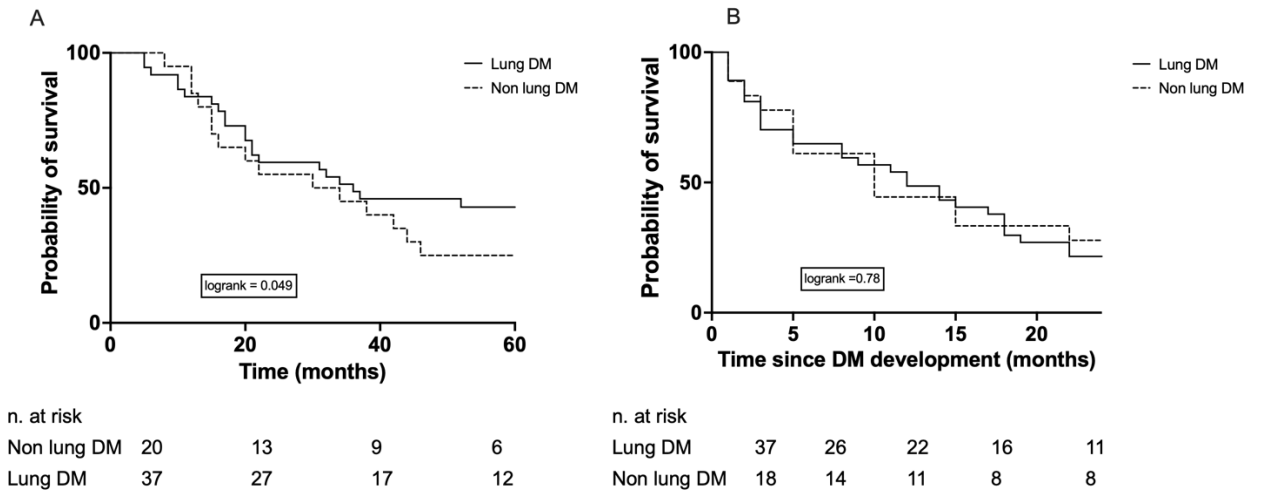
Figure 2. OS after distant progression according to p16-status.

OS = Overall Survival; DM = Distant Metastasis

The estimated median OS after progression was 10 months (3-18) for p16+ and 43 (5-76) for p16- patients, respectively (p=0.001). When exploring the impact of p16 status on 5-year OS and DM onset, the presence of HPV resulted in lower mortality (**eFigure 3, panel A, Supplementary Material**) and metastatic disease rate (**eFigure 3, panel B, Supplementary Material)** (p=0.04 and p=0.04, respectively).

Among those patients who developed DM, 37 (65%) were diagnosed with an isolated pulmonary metastasis, of which 23 (62%) were p16+, while 14 (38%) were p16-. We made a comparison between those who developed DM in the lung and those with DM onset in other sites, such as bone, liver, and non-locoregional lymph nodes, considering these as a unique group. We found that the 5-years OS was better in those who developed lung DM as compared with those who developed DM in other sites (**Figure 3A).** However, the Kaplan-Meier curve showed that the 2-years OS after distant progression did not differ significantly between the groups (**Figure 3B).** The estimated median OS after progression was 11 (2.5-24) months versus 9 (2-21.8) months for patients with DM in the lung and patients with DM in other sites, respectively (p=0.78).

Figure 3.



n. at risk				
Non lung DM	20	13	9	6
Lung DM	37	27	17	12

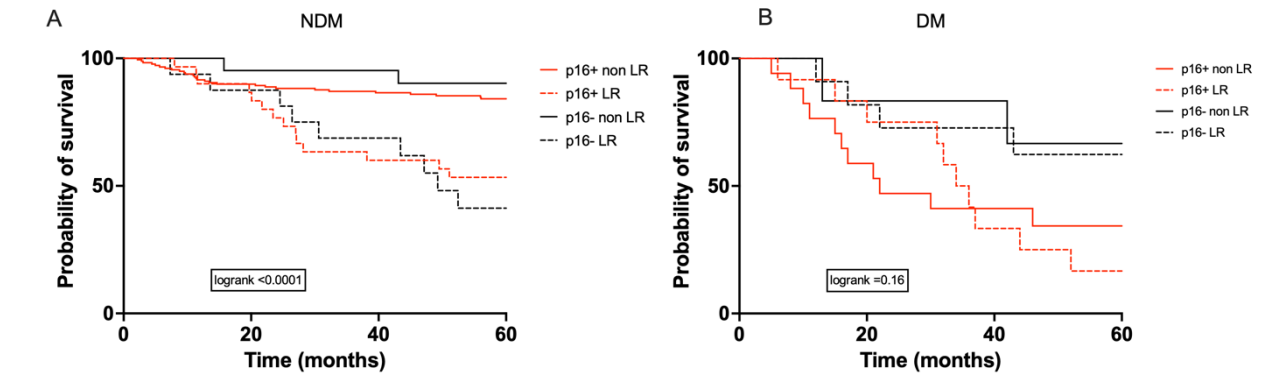
n. at risk					
Lung DM	37	26	22	16	11
Non lung DM	18	14	11	8	8

Figure 3. Panel A. 5-years OS in those with lung DM as compared with those who developed DM in other sites. Panels B. 2-years OS in those with lung DM as compared with those who developed DM after distan progression.

OS = Overall Survival; NDM = Non-Distant Metastasis; DM = Distant Metastasis.

Figure 4 illustrates the impact of LRr in combination with p16-status on OS in patients who developed DM and in those who did not. The onset of LRr significantly reduced the 5-year OS only in NDM-group (p<0.0001, **Panel A**), while no statistical significance was found in the DM-group (p=0.16, **Panel B**).

Figure 4.



n. at risk				
p16+ non LR	178	161	153	142
p16+ LR	30	27	19	16
p16- non LR	22	21	20	18
p16- LR	16	15	11	7

n. at risk				
p16+ non LR	17	11	7	4
p16+ LR	12	10	5	3
p16- non LR	6	6	6	5
p16- LR	11	10	8	7

Figure 4. Panels A-B, OS comparing the association of p16 status and occurrence of LRr, in NDM and DM groups.

OS = Overall Survival; LRr = Loco-Regional relapse; NDM = Non-Distant Metastasis; DM = Distant Metastasis.

Discussion

This study aims to identify factors capable of predicting the risk of developing DM. This knowledge would allow patient stratification at the time of diagnosis, and consequently a therapy modulation with a potential intensification for the treatment strategy in those OPSCCs more likely associated with DM occurrence.

As reported by some Authors[16], we found that p16+ OPSCCs carry a lower risk of developing DMs, when compared to p16- ones (p=0.04). Nevertheless, several studies in the literature suggest a similar incidence of DMs, regardless HPV-status[4,12,15].

Smoking is another factor that influences the risk of DMs. Our multivariable analysis shows that patients without smoking exposure have a lower probability of developing DMs, with an OR of 0.4 (p=0.04), as previously described in literature[20,21]. Tobacco smoking habits represent an independent predictor of disease progression and mortality in p16+ OPSCC. It is reported that the hazard of DM development increases by 1% per pack-year and patients with >10 pack-years have a higher likelihood of locoregional failure and death[22]. These considerations could be explained by the fact that tobacco induces epigenetic alterations and can locally suppress oral immunity that could interfere with tumor aggressiveness[23,24]. Moreover, smoking could alter the mutation profile of HPV-driven OPSCC[25]. Our results suggest that former and current smokers might deserve closer clinical-radiological evaluations to immediately detect possible DMs.

From the multivariable analysis, locally advanced diseases were found to be an independent risk factor for developing DMs. In our cohort, the DM rate in T4a/T4 group was 18.4% (33 patients out of 179), with an OR of 1.5 (p=0.04). Similar data were found by Weller et al.: comparing the T4 group with the T1-T3 one, the 5-year rate of DM was 21% versus 11%, with an HR of 2.785 (p=0.0266)[21].

As regards the cN-status, we found a significant association for the cN2c stage in p16- group. This subgroup of patients had a higher rate of DM, with an OR of 3.9 (p=0.04), but not confirmed in multivariable analysis.

T4b and cN3 stages were not significantly associated with the risk of DM development. This finding is probably due to the small cohort of patients with these characteristics (p=0.4 for both). However, we could assume that a higher tumor stage is most likely associated with worse outcomes, as reported in several studies[12,20,21,26].

The data from the multivariable analysis suggest that patients with a complete response to primary treatment have a lower risk to develop DM (OR=0.4, p=0.04).

We also confirmed the impact of LRr on the development of DM: LRr is an important risk factor for distant progression, with an OR of 4.5 (p<0.001), as reported in other studies[27,28].

It is well described in literature and also reported in this study, that patients with DM have a worse OS compared to the NDMs group (p<0.0001)[29].

We tried to identify if there is a different impact of DM on 5-years OS between p16+ and p16- OPSCC groups. The cohort of p16+ tumors, which develop DM, have significantly poorer outcomes (p<0.0001) compared to NDM-group. This result may be related to a better response to chemo-radiation therapy of the p16-group that allows a greater loco-regional control compared to the p16- OPSCC[4,30]. As shown in literature, the main cause of death in the HPV-related OPSCC is represented by DM development[11,15]. In the p16- OPSCC group, we reported similar 5-year OS in patients who developed DM and those who did not (p=0.3). This result might be related to a more loco-regional aggressive disease of p16- tumors resulting in a lower loco-regional response to the primary treatment[6]. The impact of DMs on p16+ group is further underlined considering 2-years OS after distant progression: when DMs occur the two groups seem to evolve as the same disease (p=0.06), with a survival trend in favor of p16- tumors.

As confirmed by the literature, we found that the most frequent site for DM in OPSCC is the lung[6,11,15]. A different 5-years OS was observed between the lung metastasis group and the non-pulmonary ones. The DM cohort with lung metastasis has a better 5-years OS (p=0.049). However, this result is not observed after distant progression occurrence, with 2-years OS curves showing no significant difference between the two groups. These data could be explained by the possibility of performing radical approaches on pulmonary lesions, such as surgery or stereotactic radiation[31,32].

In our study, the experience of an LRr did not correlate with statistically significant results in terms of OS in the DM group (p=0.16), but only in the NDM ones (p<0.0001). However, in the DM group, we pointed out a trend showing worse OS for patients with positiveness for p16 when compared with p16- ones, regardless LRr development. Some Authors reported that the presence of an LRr may be a predictor of developing DM, despite excellent loco-regional control of the recurrence[33].

This study has some limitations. Firstly, the retrospective design makes the results prone to recall bias or misclassification bias. Secondly, the wide time frame covered by the study includes diagnostic-therapeutic approaches that changed over time (i.e., TNM and guidelines). Finally, the subdivision of these patients into different subgroups (e.g., cN-status) compared to the sample size led us to observe trends that could have been statistically significant with a greater number of patients.

CONCLUSION

This retrospective study shows a possible stratification of patients based on the risk of DM development.

Firstly, we found that p16+ OPSCC, patients who never smoked, and those with a complete response after the first treatment carry a lower risk of developing DM.

Advanced stage OPSCC (cT4/cT4a), both p16+ and p16-, and patients with LRr have an increased risk of DM. Although no statistical significance has emerged, nodal involvement, especially in p16- group, also showed a trend of developing DM.

Developing DM has a different impact on OS between the two groups: p16+ OPSCC, which develop DMs, have significantly higher mortality than NDM-group while this impact is not equally observed in the p16- group.

Furthermore, lung metastases have a better prognosis compared to other sites, thanks to the possibility of metastasis-directed therapy.

Considering the main predictors of OS among the two groups, further studies are needed to determine the best loco-regional treatment in p16- OPSCC and factors correlated to worse treatment response in p16+.

Appendix – Supplementary materials

Figure e1.

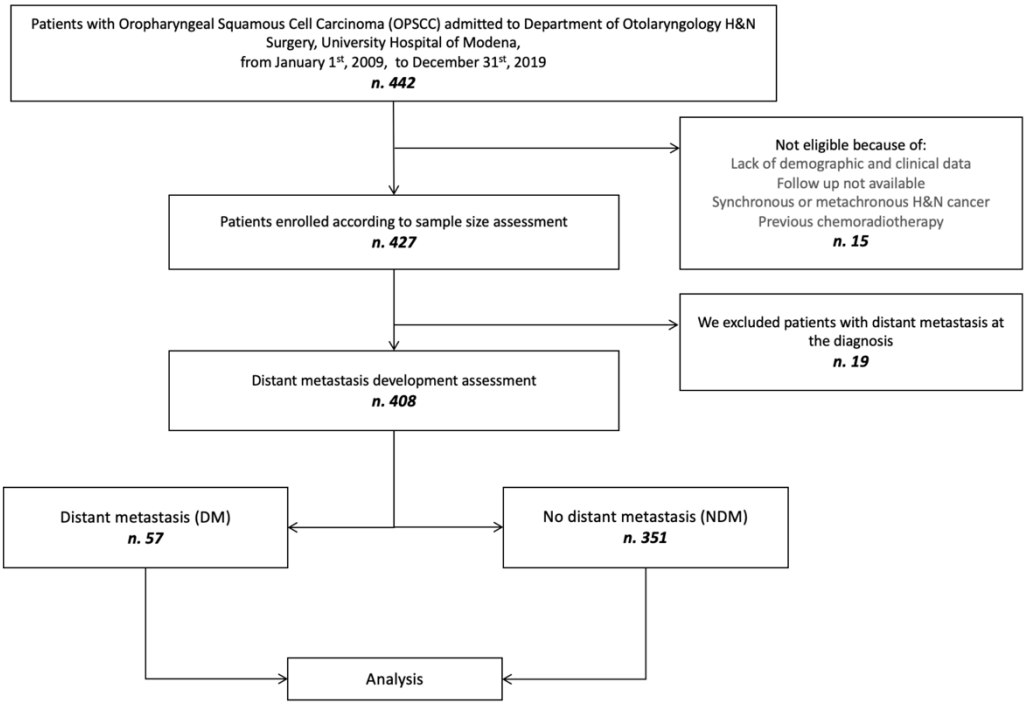


Figure e1. Flowchart with decision-making for patients enrolled.

Figure e2.

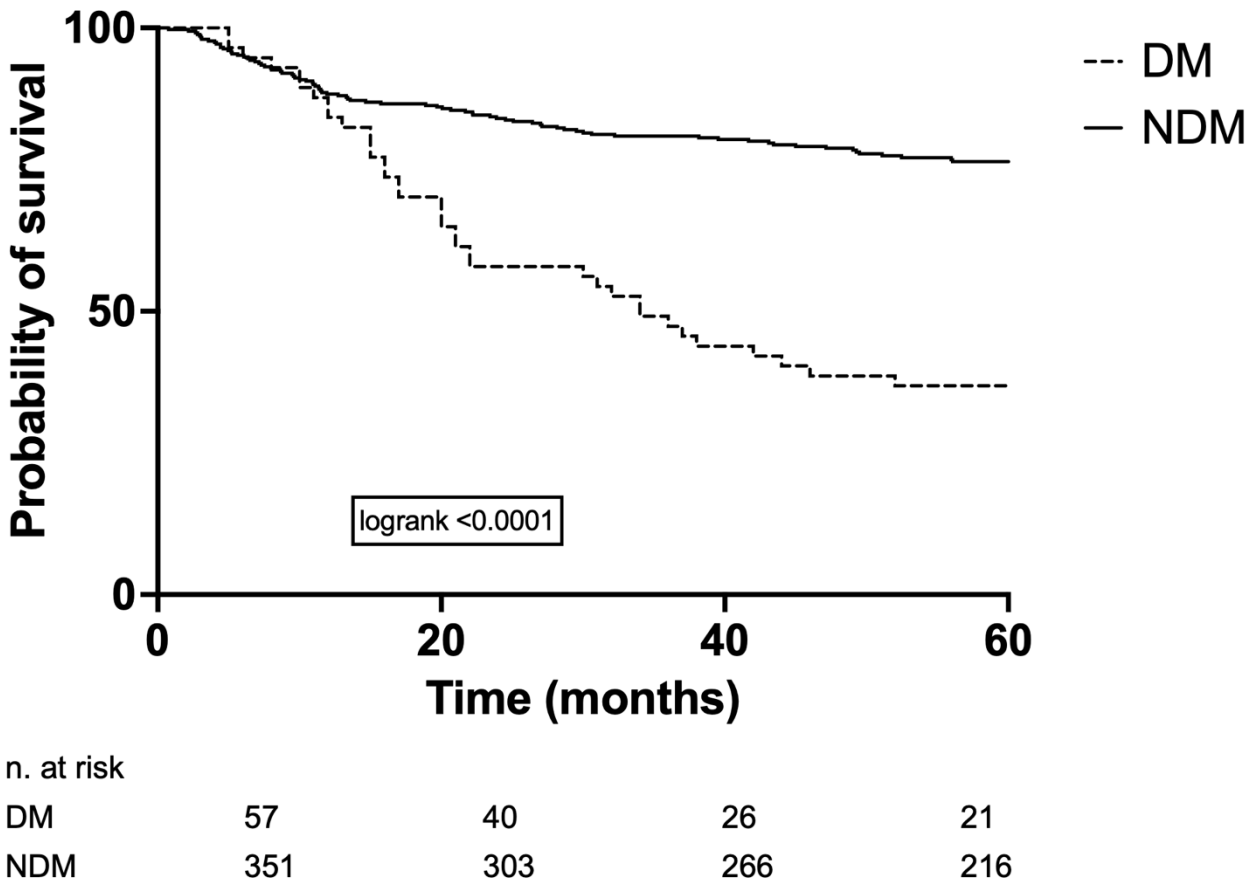
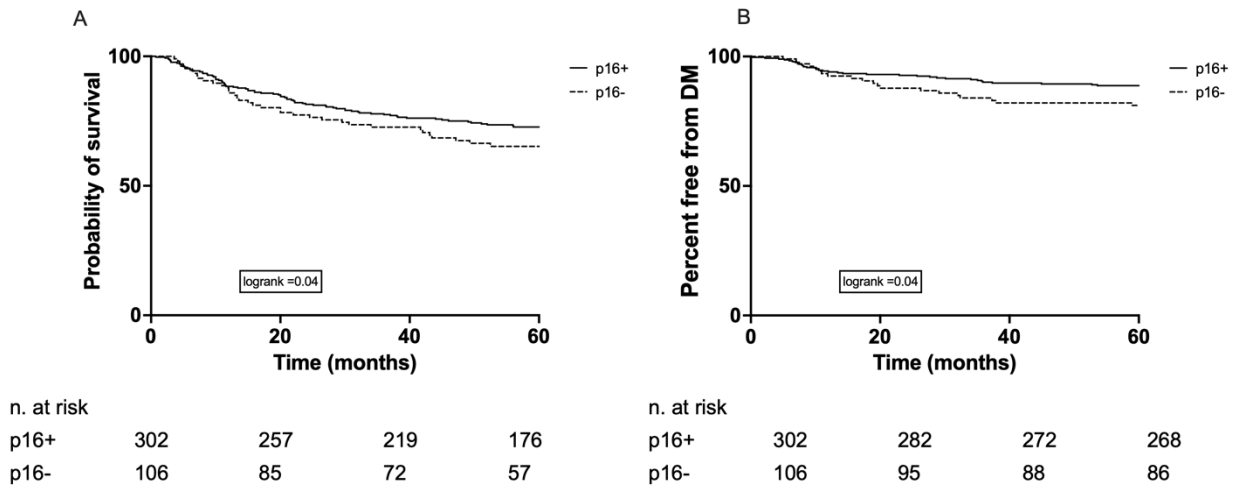


Figure e2. OS between DM and NDM groups.

OS = Overall Survival; NDM = Non-Distant Metastasis; DM = Distant Metastasis.

Figure e3.



n. at risk				
p16+	302	257	219	176
p16-	106	85	72	57

n. at risk				
p16+	302	282	272	268
p16-	106	95	88	86

Figure e3. Panel A, OS between p16+ and p16- groups. Panel B, DM development rate comparing p16+ and p16- groups. OS = Overall Survival; DM = Distant Metastasis.

OS = Overall Survival; NDM = Non-Distant Metastasis; DM = Distant Metastasis.

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Chapter 4.

Integrated endoscopic treatment of primitive unresectable tracheal tumor: the INTACT retrospective cohort study

Abstract

Objectives

Primitive tracheal tumors represent a rare entity whose management, when resection results unfeasible, remains challenging for clinicians. Primary aim of this study was to explore the survival and the factors influencing prognosis of patients with unresectable primitive tracheal tumor undergoing multimodal treatment integrating interventional bronchoscopy and radiotherapy.

Materials and methods

This retrospective cohort study was conducted at the University Hospital of Modena (Italy) over a 10-year period (January 2010-January 2020) analyzing patients with primary tracheal tumor receiving interventional bronchoscopy plus radiotherapy. Survival analysis was conducted for the whole population and according to histology, development of metastasis, stent placement and the onset of disease relapse. The raw and independent association between potential risk factor and 5-year mortality and the reported complications were investigated.

Results

A total of 12 patients were included. Five-year survival rate was 42% with a median survival time of 26.7 (4.1 – 82) months. Survivors showed a higher prevalence of cystic-adenoid histology (80% VS 14%, p=0.07), while patients who were dead at 5 years were those with a more advanced T (prevalence of T2 71% VS 0%, p=0.03) and a lower response to first line treatment (57% VS 0%). Treatment complications accounted for stent dislocation (33%) and the onset of granuloma (18%), while no major side effects were reported. The presence of cystic-adenoid histology resulted in significantly improved 5-year survival rate (80% versus 14%, p=0.01). The onset of distal metastasis, the occurrence of disease relapse and the placement of tracheal stent did not result significantly associated with lower survival. Among analysed variables, only the presence of cystic-adenoid histology resulted independently associated with survival (OR=0.1, p=0.04).

Conclusions

Multimodal treatment including interventional bronchoscopy and associated radiotherapy for unresectable primary tracheal tumors seems not burdened by significant complication and may provide benefits in terms of survival for those patients with cystic-adenoid histology.

Introduction

Primary tracheal tumors are rare entity, constituting approximately 0.1- 0.4% of malignant diseases[1]. Although most of tracheal tumors affecting adults are malignant (90%), in children these tumors appear even rarer and mostly consist of benign diseases (only 10-30% of malignant tumors). Malignant disease of the trachea can arise from different structures such as respiratory epithelium, salivary glands, connective tissue and others, but from a histological point of view, squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC) account for about two-thirds of all the adult primary tracheal tumors[2]. Symptoms are typically due to central airway obstruction, and appear late, when the tumor has already involved most of the tracheal lumen[3]. Timely diagnosis remains a major clinical challenge for improve patients' survival. Indeed, symptoms are often mistaken for those of other respiratory diseases such as asthma or obstructive pulmonary disease (COPD), resulting in diagnosis delay, when the disease is at an advanced stage and sometimes beyond the scope of curative treatment[4]. Surgical resection supplemented by postoperative radiotherapy are the treatment of choice to achieve long-term survival and relieve airway obstruction[5]. Patients not suitable for surgery are managed with definitive radiation therapy, although ACC_s are typically less radiosensitive as compared with another primitive tracheal tumor such as SCC_s[6]. Interventional pulmonology techniques, such as intraluminal debulking of the tumor supported by laser therapy with or without stent, are usually considered to have a role in palliation for patients suffering from unresectable tumors, or in a setting of emergency therapy prior to definitive treatment in patients with acute respiratory distress due to significant central airway obstruction[3]. Retrospective national analysis conducted in England on management and prognosis of primary tracheal cancer, suggest that performing interventional bronchoscopy by itself is an independent and significant survival variable[7]. However, due to the lack of significant data on this topic, due to different biological behavior across the different histotypes, the real impact on patients' survival of an integration of interventional pulmonology technique with adjuvant radiotherapy in unresectable patients is not known. Being that the extension of the disease to adjacent organs, the size of the tumor at the time of diagnosis, and the health of the patients not rarely rule out the possibility of surgery, data that can define the role of operative bronchoscopy integrated with radiotherapy in the definitive treatment of tracheal cancer are needed. The primary explorative aim of this retrospective analysis was to report the 5-year survival rate of patients with primitive tracheal tumor undergoing interventional

bronchoscopy plus chemotherapy/radiotherapy (integrated treatment). Factors influencing prognosis were further investigated as secondary aim.

Materials and methods

Design

INTACT is a retrospective, monocentric cohort study carried out at the Diagnostic and Interventional Bronchoscopy Unit of the University Hospital of Modena (Italy). Approval from Local Ethics Committee (Prot. AOU 0013040/19 and 276/2019/OSS/AOUMO) and consent to publish data were obtained as appropriate.

Population and measures

To build the study population we queried the local registry of the Bronchoscopy Unit of the University Hospital of Modena (Italy) where clinical, endoscopic, and radiological data of patients consecutively referred since January 2010 are collected. Inclusion criteria were applied to the time frame January 2010-2022 and were as follows: age >18 years, cytologic and/or histologic diagnosis of primitive tracheal tumor. All patients had undergone flexible bronchoscopy whose reports were considered, alongside computed tomography (CT) scan images, in order to confirm primitive tracheal tumors. Patients were excluded if aged > 80, performance status $\leq$ 2 and/or with end-stage chronic obstructive pulmonary disease, interstitial lung disease, life-threatening stenosis requiring urgent endoscopy, open surgery treatment received.

Chart review, health record, medical record, archival data analysis was further performed. The following data were collected: demographic data, Charlson Index for comorbidity assessment, histopathology, genetic analysis of the tumor (EGFR and KRAS mutations, ALK translocations), PD-L1 expression, type of anticancer treatment received (chemotherapy, radiotherapy, tyrosine kinase inhibitors, immunotherapy), complications of endoscopic treatment, 5-year survival. All interventional procedures were 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. Whenever indicated, a silicone stent (NOVATECH Doumon stents, Boston Medical Products, Inc., Westborough, MA, USA) was placed. All patients with primitive tracheal tumor with airway stenosis > 50% were treated with interventional bronchoscopy before radiotherapy treatment (60

Gy) independently from the onset of symptoms. All disease recurrences with airway stenosis > 50% were treated with endoscopic re-intervention.

Statistical Analysis

Baseline characteristics of the enrolled patients were described as a whole and according to the 5-year survival status. T-test and Wilcoxon-Mann-Whitney test served for continuous variables, whereas categorical variables were compared by $\chi 2$ test or Fisher's exact test, as appropriate.

The 5-year survival analysis was performed with participants' follow-up accrued from the date of diagnosis until death. The association between demographic and clinical characteristics with 5-year survival was tested using univariable and multivariable logistic regression model. In post-hoc sensitivity analyses, the 5-year survival was assessed according to histology, development of distal metastasis, silicone stent positioning and the onset of relapse. In another sensitivity analysis the impact of cystic-adenoid histology on 5-year survival was analyzed through unadjusted and adjusted Cox proportional hazard regression model. Significance was set for p values < 0.05. Statistics were performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Population

A total amount of 13792 patients were referred to the Bronchoscopy Unit of the University Hospital of Modena (Italy) within the pre-specified period of interest. Out of them, 20 (0.15%) presented with primitive tracheal tumor and 12 (0.09%). resulted eligibile. Study flow-chart is shown in **Figure 1**. The median follow-up from diagnosis was 27 (IQR= 4 – 60) months.

Figure 1.

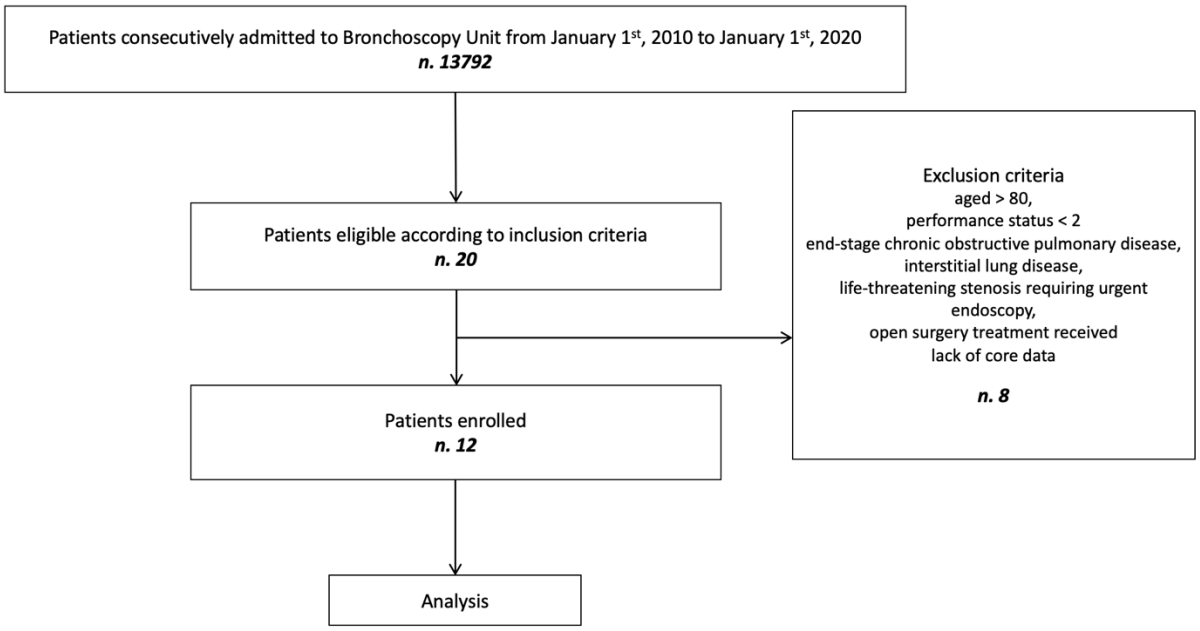

Figure 1. Study flowchart.

Demographics, clinical features, and oncological therapies are presented in **Table 1**. At 5 years, 5 patients (42%) were alive while 7 (58%) were dead. Two out of 5 patients who survived presented expression of mTOR (one associated to androgen receptors) while one patient expressed c-KIT. Among those who were dead at 5 years, 2 patients expressed PD-L1 (one associated to ROS1), one patient showed the expression of Ki67/MIB and one patient had K-RAS mutated. The two groups did not show differences in terms of demographic characteristics and modality of standard treatment (**Table 1**). Survivors showed a higher prevalence of cystic-adenoid histology (80% VS 14%, p=0.07), while patients who were dead at 5 years were those with a more advanced T (prevalence of T2 71% VS 0%, p=0.03) and a lower response to first line treatment (57% VS 0%). Treatment complications accounted for stent dislocation (33%) and the onset of granuloma (18%)

and were not different among groups. Non major complications (i.e. massive bleeding and/or stent occlusion and/or fistulas) were reported.

Table 1.

Variable	Overall n=12 (100)	Alive at 5 years n= 5 (42)	Death at 5 years n = 7 (58)	p value
Age at diagnosis, years (IQR)	62 (49 – 67.3)	50 (46 – 61)	63 (55 – 71)	0.15
Male sex, n (%)	6 (50)	2 (40)	4 (57)	0.99
Smoker status				
Never, n (%)	5 (42)	3 (60)	2 (29)	0.29
Former, n (%)	5 (42)	2 (40)	3 (43)	0.99
Active, n (%)	2 (18)	0 (0)	3 (43)	0.23
Histology				
Cystic-adenoid carcinoma, n (%)	5 (42)	4 (80)	1 (14)	0.07
Squamous cell carcinoma, n (%)	3 (24)	1 (20)	2 (29)	0.9
Other, (%)	4 (33)	0 (0)	4 (57)	0.08
cT				
cT0 o cTIS, n (%)	0 (0)	0 (0)	0 (0)	---
cT1, n (%)	4 (33)	3 (60)	1 (14)	0.22
cT2, n (%)	5 (42)	0 (0)	5 (71)	0.03
cT3, n (%)	3 (24)	2 (40)	1 (14)	0.52
E				
E1, n (%)	3 (24)	2 (40)	1 (14)	0.52
E2, n (%)	2 (18)	0 (0)	2 (29)	0.47
E3, n (%)	7 (58)	3 (60)	4 (57)	0.99
cN				
N0, n (%)	4 (33)	3 (60)	1 (14)	0.22
N1, n (%)	4 (33)	1 (20)	3 (43)	0.58
N2, n (%)	4 (33)	1 (20)	3 (43)	0.58
M				
M0, n (%)	9 (76)	3 (60)	6 (86)	0.52
M1, n (%)	3 (24)	2 (40)	1 (14)	0.52
Carinal involvement, n (%)	4 (33)	1 (20)	3 (43)	0.58
Treatment				
Stent placement, n (%)	9 (76)	3 (60)	6 (86)	0.52
RT, n (%)	12 (100)	5 (100)	7 (100)	---
CHT, n (%)	10 (83)	4 (80)	6 (86)	0.99
Number of endoscopic treatment, n (%)	2 (1 – 3)	3 (2 –5)	2 (1 – 2.5)	0.17
Complications				
Granuloma	2 (18)	1 (20)	1 (14)	0.8
Stent dislocation	4 (33)	2 (40)	2 (29)	0.6
Stent occlusion	0 (0)	0 (0)	0 (0)	0.9
Major endotracheal bleeding	0 (0)	0 (0)	0 (0)	0.9
Tracheal injury/fistulation	0 (0)	0 (0)	0 (0)	0.9
CT response after treatment				
Disease reduction, n (%)	3 (24)	3 (60)	1 (14)	0.22
Stable disease, n (%)	5 (42)	2 (40)	2 (29)	0.99
Disease progression, n (%)	4 (33)	0 (0)	4 (57)	0.08

Relapse, n (%)	10 (83)	3 (60)	7 (100)	0.15
Time to relapse, months (IQR)	3 (2.3 – 16.8)	18 (15.5 – 20)	3 (1.5 – 3)	0.01
Survival time, months (IQR)	26.7 (4.1 – 82)	91.3 (78.3 – 93)	4.6 (2.7 – 8.1)	0.002

Table 1. General and clinical features of the study population presented as a whole and according to 5-year survival status. Data are presented as number and percentage for dichotomous values or median and IQR for continuous values.

IQR = Inter Quartile Range; CT = computed tomography; RT = Radiotherapy; CHT = Chemotherapy

Survival analysis

Five-year survival for the whole population is illustrated in **Figure 2** by means of Kaplan-Meier curves. Five-year survival rate was 42% (5/12).

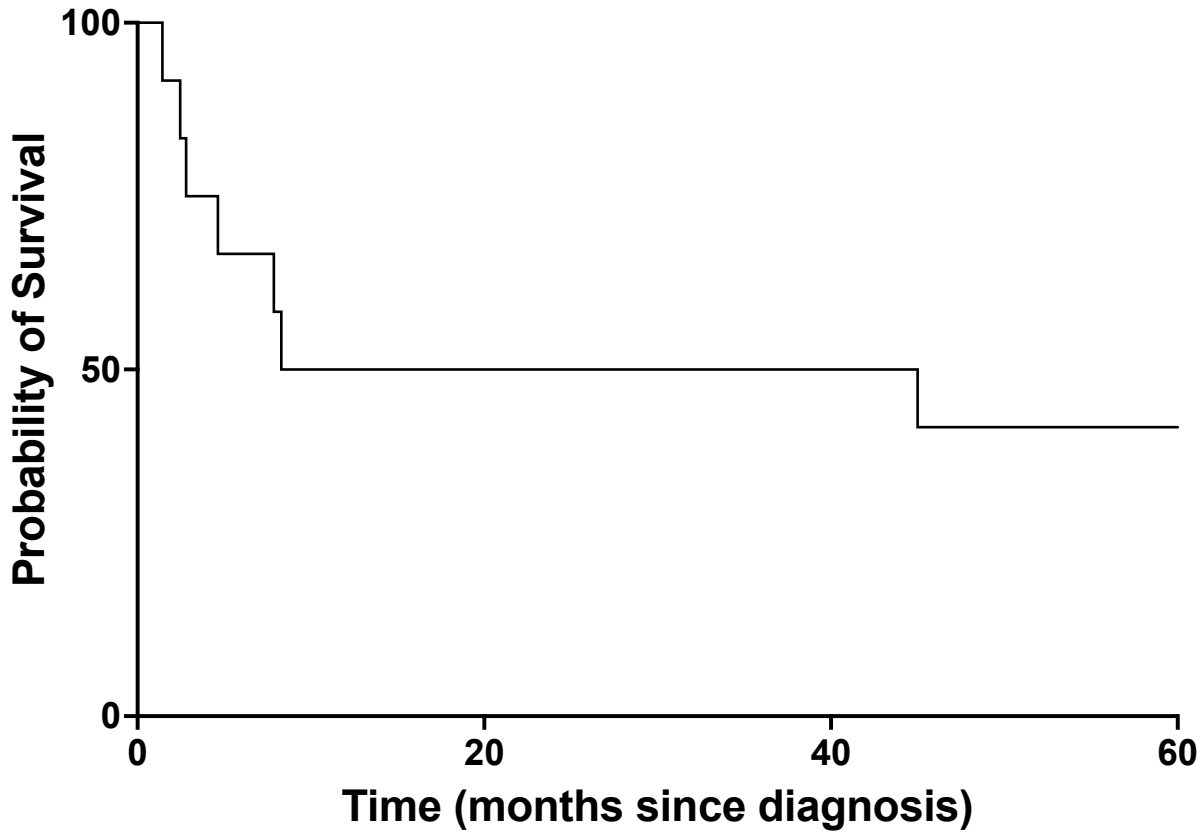

Figure 2. Kaplan-Meier estimates showing 5 years survival for the whole population.

Table 2 reports the demographic and clinical features associated with 5-years mortality. Among analysed variables, only the presence of cystic-adenoid histology resulted independently associated with survival (OR=0.1, p=0.04).

Table 2.

	Univariable			*Multivariable*		
Parameter	***OR***	***95% Confidence Interval***	**p value**	***OR***	***95% Confidence Interval***	**p value**
Age at diagnosis, years (IQR)	0.9	0.98 – 1.28	0.15			
Male sex, n (%)	2	0.25 – 16.3	0.99			
Smoker status						
Never, n (%)	0.33	0.03 – 1.97	0.29			
Former, n (%)	1.1	0.12 –7.49	0.99			
Active, n (%)	8	0.56 – 43.1	0.23			
Histology						
Cystic-adenoid carcinoma, n (%)	0.04	0.003 – 0.88	0.07	0.1	0.019 – 0.98	0.04
Squamous cell carcinoma, n (%)	1.6	0.14 – 28.4	0.9			
Other, (%)	12	1.1 – 72	0.08			
cT						
cT0 o cTIS, n (%)	---	----	---			
cT1, n (%)	0.1	0.01 – 1.36	0.22			
cT2, n (%)	21	1.6 – 154	0.03			
cT3, n (%)	0.25	0.02 – 3.19	0.52			
E						
E1, n (%)	1.25	0.02 – 3.19	0.52			
E2, n (%)	4.5	0.34 – 21.3	0.47			
E3, n (%)	0.89	0.1 – 7.11	0.99			
cN						
N0, n (%)	0.11	0.01 – 1.36	0.22			
N1, n (%)	3	0.29 – 47.4	0.58			
N2, n (%)	3	0.29 – 47.4	0.58			
M						
M0, n (%)	4	0.31 – 66	0.52			
M1, n (%)	0.25	0.02 – 3.19	0.52			
Carinal involvement, n (%)	3	0.29 – 47.4	0.58			
Treatment						
Stent placement, n (%)	4	0.31 – 66	0.52			
RT, n (%)	---	---	---			
CHT, n (%)	1-5	0.06 – 32.7	0.99			

Number of endoscopic treatment, n (%)			
CT response after treatment			
Disease reduction, n (%)	0.11	0.01 – 1.36	0.22
Stable disease, n (%)	0.6	0.07 – 5.69	0.99
Disease progression, n (%)	14	1.1 – 72	0.08
Relapse, n (%)	4.5	0.72 – 51	0.15
Time to relapse, months (IQR)	0.75	0.25 – 0.92	0.01

Table 2. Raw and independent association between demographic and clinical features and the development of metastasis. Association is shown through odds ratio (OR) and 95%CI.

Figure 3 illustrates the 5-year survival according to histology (panel A), the development of distal metastasis (panel B), the endoscopic placement of stent (panel C) and the disease relapse within follow-up (panel D). The presence of cystic-adenoid histology resulted in significantly improved 5-year survival rate (80% versus 14%, p=0.01). The onset of distal metastasis and the placement of tracheal stent did not result significantly associated with lower survival (p=0.5 and p=0.6 respectively). The survival rate among those who did not experience disease relapse was 100%.

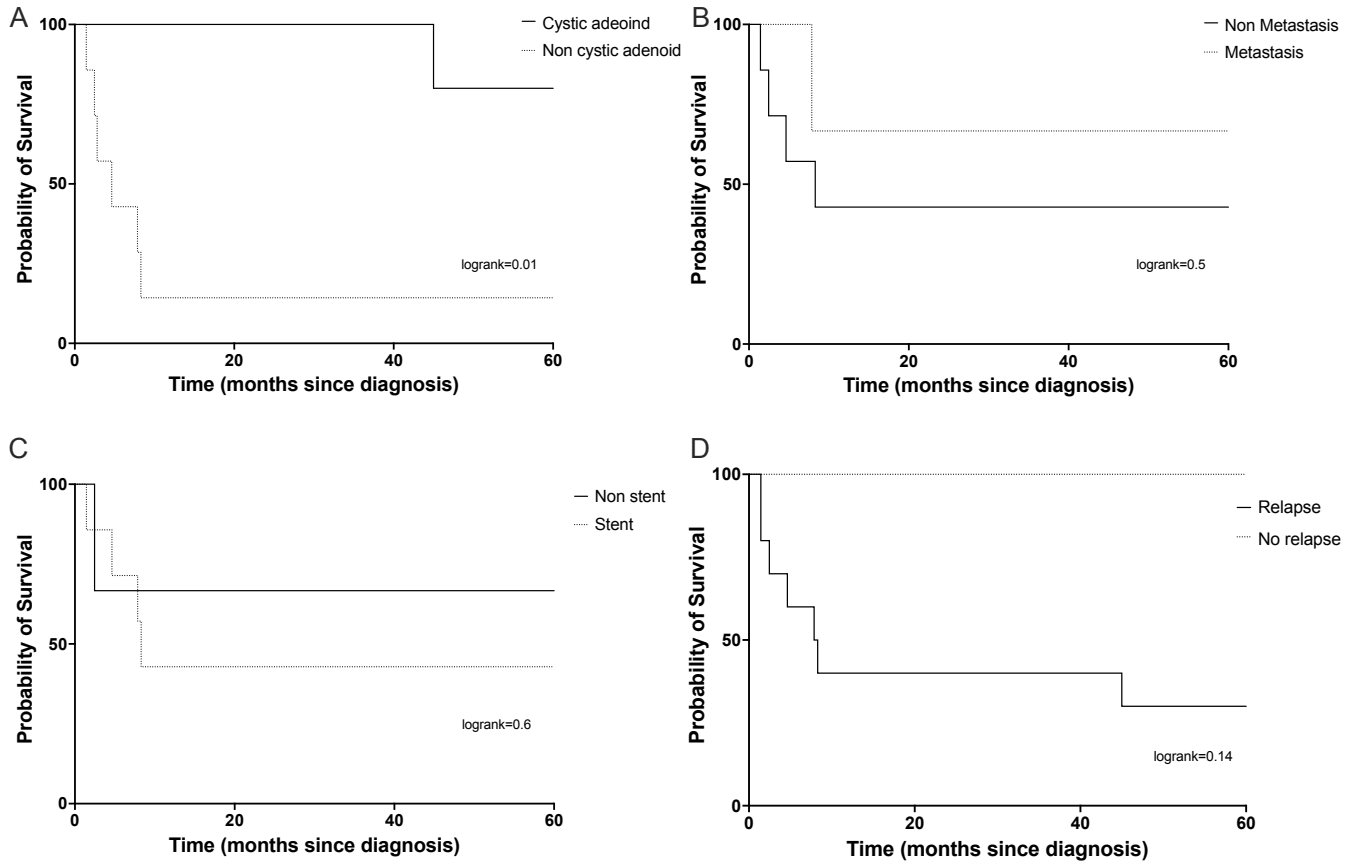

Figure 3. Panel A. Five-years survival in those with cystic adenoid tracheal tumor as compared with those with other histology. **Panel B**. Five-years survival in those who developed distal metastasis as compared with those who developed did not. **Panel C**. Five-years survival in those who underwent stent positioning as compared to those with no tracheal stent. **Panel D**. Five-years survival in those who experienced disease relapse as compared to those who did not.

Figure 4 illustrates the relapse-free survival time (panels A and B) and the median time to the first relapse (panel C and D) according to histology and endotracheal stent placement. Since diagnosis, the relapse-free survival was not different between patients with cystic adenoid tracheal tumor and those with other histology (p=0.12) while the time to the first disease relapse was significantly higher in those with cystic adenoid histology (18 [14.3 – 21] months versus 2.5 [1 – 3] months, p<0.001). Stent placement did not affect relapse-free survival at 5 years (p=0.67) nor the time to the first disease relapse (3 [1.5 – 18] versus 7.5 [2 – 13] months, p=0.87).

Figure 4.

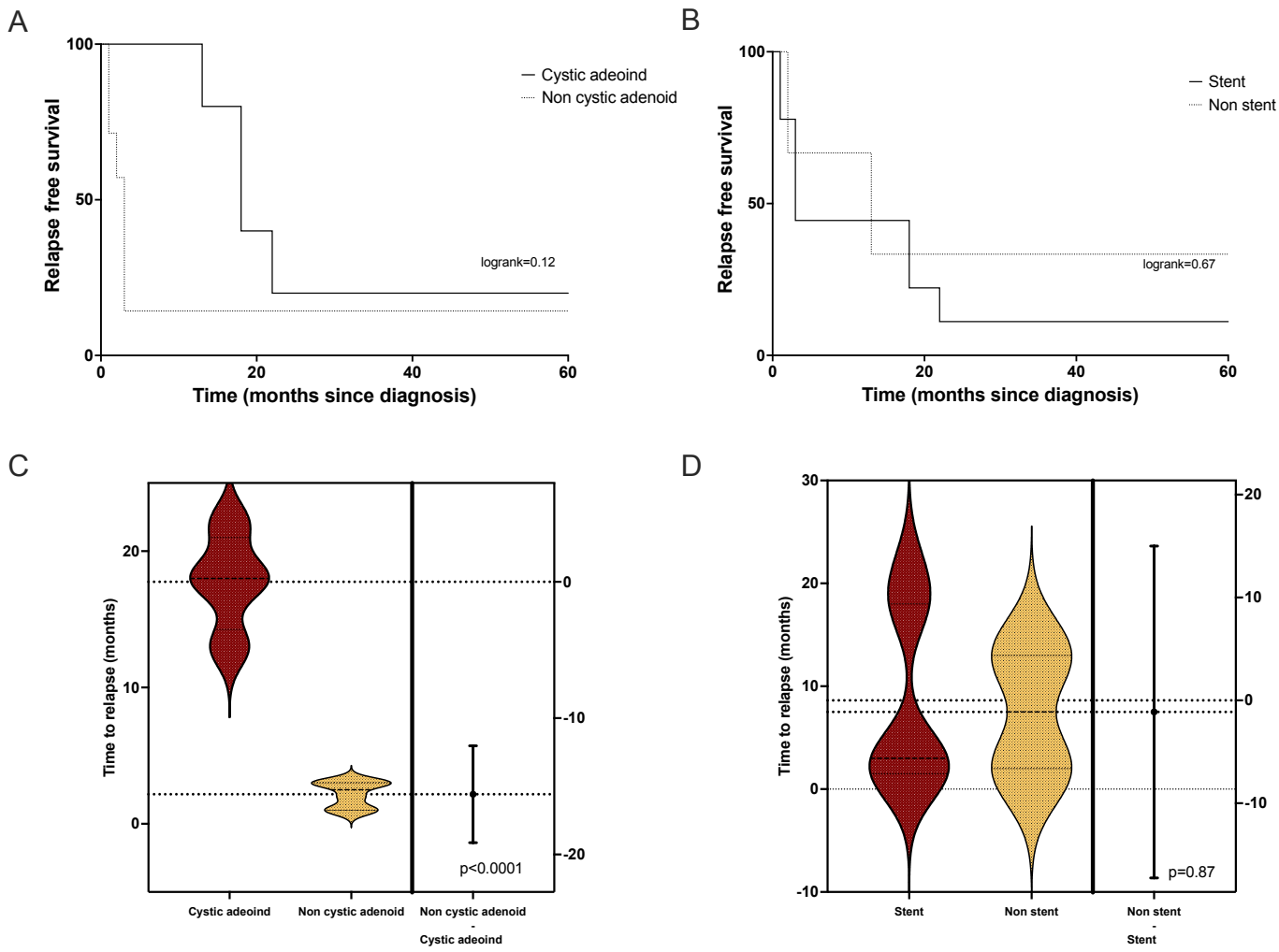

Figure 4. Panel A. Five-years disease-free survival in those with cystic adenoid tracheal tumor as compared with those with other histology. **Panel B**. Five-years disease-free survival in those who underwent tracheal stent placement as compared to those who did not. **Panel C**. Comparison of the time to first disease relapse between those with cystic adenoid tracheal tumor as compared with those with other histology. **Panel D**. Comparison of the time to first disease relapse between those who underwent tracheal stent placement as compared to those who did not

Discussion

Despite obvious limitations, this study suggests that the integration of interventional bronchoscopy with radiotherapy, also used outside palliation purpose to relieve airway obstruction, may achieve long-term survival benefits in patients suffering from unresectable tracheal tumor with ACC histology (80% 5-years survival rate). Furthermore, endoscopic tumor resection, can be repeated in case of local recurrence to maintain airway patency without significant side effects. Our series showed that the onset of complications after multimodal treatment was not significant. The main side effect was represented by stent dislocation (33%) that was not associated with respiratory failure or tracheal occlusion and was successfully managed with re-intervention. Moreover, major complications such as massive tracheal bleeding, fistulas or tracheal injury were not reported.

Primary tracheal cancers are rare subset of tumors, therefore studies investigating the management of this disease are retrospective and analyze small patient populations. The low incidence of tracheal tumors has obviated prospective studies to evaluate and compare therapy. However, tracheal cancer surgical resection constitutes the gold standard to achieve long term survival. A retrospective study by Gaissert et al showed that resection of trachea or carina is associated with long-term survival when compared to primary radiotherapy and/or palliation, particularly for patients with complete resection, negative airway margins, and ACC[9]. The reported overall operative mortality was 7.3% and improved each decade from 21% to 3%, probably due to improvements in surgical techniques[9]. The benefit of surgical treatment is less clear when resection is incomplete, while the presence of lymph nodes metastases did not seem to decrease survival after surgery[10 -11]. Furthermore, in ACC for its peculiar behavior characterized by more indolent but progressive local growth, resection provides excellent palliation even in patients with distant metastases[12]. However, tumor size at the time of diagnosis, patient's clinical conditions and comorbidities may limit the possibility of surgery, thus a considerable proportion of patients cannot benefit from the treatment of choice and are treated with definitive radiotherapy[13]. Definitive radiotherapy showed a survival benefit when compared to palliative treatment, especially in patients with SCC histology[6]. However, study by Xie L et al showed a 5-year overall (OS) survival of 22.7% in patients treated with definitive radiotherapy for unresectable tracheal tumor versus 55% in patients underwent surgery plus radiotherapy[6]. Studies focused only on unresectable ACCs, a histotype considered poorly radiosensitive, showed 5-year OS ranged

between 17% to 56% after definitive radiotherapy, with significant worse outcome when compared to patients underwent surgery[14-16]. More recently, retrospective data from French and Germany studies show no significant difference between operated and non-operated patients with ACCs, with 5-year OR of 82-92% after definitive radiotherapy[17,18]. However, local relapse were observed mainly in non-operated patients, raises the question of combining radiosensitising agent such as platinum-based combination, or interventional endoscopic technique to control intraluminal tumor growth. Given that ACCs are generally considered chemoresistant, and target therapies currently have no indication in localized tumor, interventional bronchoscopy with endoscopic resection can be a rational treatment to obtain a debulking of the endocanalicular tumor, both before definitive radiotherapy and in case of local recurrence. In our series, interventional bronchoscopy techniques (with or without stent placement) were performed in all patients with > 50% obstruction of the airway lumen before definitive radiotherapy regardless of symptoms, therefore outside palliative proposal. Being considered palliative, endoscopic intervention is often performed when significant symptoms are present, and the degree of obstruction is very severe; thus, the risks of the intervention can be relevant. Indeed, computational fluid dynamic study showed that the pressure drops trough airway stenosis, the physical mechanism behind the dyspnea, increase dramatically only if > 70% of the tracheal lumen was occluded[19]. The present study suggests that integration of interventional bronchoscopy plus radiotherapy may have a significant impact on survival in patients suffering from ACCs compared to other primary tracheal cancer treated with the same modality. This result can certainly be attributed to the biological features of ACC, which is generally considered a low-grade malignant tumor despite its ability to metastasize and recur locally. However, all patients with ACC enrolled in the present study required multiple endoscopic procedures for local recurrence during the 5-year follow-up, despite definitive radiotherapy treatment with radiation doses over 60 Gy. This finding may suggest that local control of recurrence by interventional bronchoscopic technique may play a significant role in the survival gain in ACC patients, justifying the high OS found in our study. Furthermore, maintain airway patency may play a key role in life expectancy also in ACC patients affected by distal metastasis, considering the slowly progression of the extra-tracheal spread of the disease, which occurs often over several years. Another result suggested of this study concerns the low impact of tracheal stenting both on 5-year survival and on disease recurrence. SPOC trial was the first randomized controlled trial investigated the potential benefit of silicone stent insertion in symptomatic malignant airway obstruction due to non-small cell lung cancer

without extrinsic compression[20]. In the SPOC trial silicon stent clearly reduced relapses by offering a “barrier effect”, but there was no significant impact on survival. The results found in our series suggest that the poor effect of stent placement on recurrence may be due to the different biological behavior of primary tracheal tumors. Indeed, ACC spread through direct extension, submucosal or perineural invasion, often recurring even after surgery. Thus, it is probable that through these local spreading mechanisms ACC may invalidate the “barrier effect” of stent placement. Furthermore, in more aggressive histotypes of primary tracheal tumors, stent may not be sufficient to stem the rapid growth of the tumor within the airways. Our study has several limits. First, the retrospective design, the reduced sample and the lack of a control group does not allow definitive conclusions on the analyzed treatment. Second, patients have been treated in center with high expertise in interventional pulmonology, therefore the validity of data cannot be extrapolated for all. Notwithstanding, our results suggest that interventional bronchoscopy should be considered early as an integral part of management of patients suffering from unresectable primitive tracheal tumors; and should be also re-propose in case of recurrence, being burdened by very few side effects. However, considering the rarity of tracheal tumors, multicenter or nationwide study is warranted to validate these finding in non-resectable tracheal tumors.

Conclusions

Multimodal treatment including interventional bronchoscopy and associated radiotherapy for unresectable primary tracheal tumors seems not burdened by significant complication and may provide benefits in terms of survival for those patients with ACC histology. These results require confirmation in larger series.

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General discussion

Notwithstanding the increased range of therapeutic options and techniques, the proper management of neoplastic and non-neoplastic airway diseases remains challenging for clinicians. Multimodality approach seems advisable, with the aim to achieve long-term effects in terms of disease control and quality of life. The research question conducted through the studies illustrated within this project confirms the need to integrate competence in the management of this kind of patients with the aim to provide tailored treatments that consider the expertise of the team. Herein we briefly discuss the main findings of each study.

Central Airway Obstructions

A proportion of IIIB NSCLC has a central airway obstruction that can occur at onset or during the course of the disease (1). 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 patient survival. Interventional bronchoscopy allows for rapid recanalization of airway obstruction, and it can be useful in locoregional control, integrating with chemo-radiant treatment in patients with locally advanced NSCLC (2). 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 centres (2,3). Although the role of interventional bronchoscopy in the palliation of symptoms is well recognized, no reliable data are currently available on the prognostic impact in the use of this technique in the multimodality management of stage IIIB NSCLC. In our study we showed that the integration of interventional bronchoscopy in the management of locally advanced NSCLC with CAO, especially when proposed early, not only has a palliative purpose but also has a significant impact on the patient's prognosis, showing a clear 1-year survival advantage for the same stage of disease. Moreover, we have shown that greater gain in life expectancy is closely related to anatomical (airway occlusion> 65%, no left mainstem obstruction) and molecular (KRAS-mutant NSCLC) cancer features.

With reference to primitive tracheal tumors, we showed that multimodal treatment including interventional bronchoscopy and associated radiotherapy for unresectable primary tracheal tumors seems feasible and may provide benefits in terms of survival especially for patients with cystic-adenoid histology. The results from our series showed that endoscopic tumor resection can be repeated in case of relapse to achieve airway patency, given that the onset of reported complications after multimodal treatment was not significant.

Benign tracheal stenosis

To date, there is no definitive consensus on the endoscopic management of tracheal stenosis not eligible for surgery. The role of endoscopic treatment of airway stenosis has been progressively increasing due to its limited invasiveness, even though this approach is burdened by frequent relapses. (4). Endoscopic management of benign airway stenosis is successful in the majority of patients, if patients are selected properly. Given its clinical effectiveness and low complication rate, endoscopic management should remain the first option for subglottic and tracheal stenosis. Endoscopic management does not preclude the use of open surgical procedures, if necessary (5). In our study, success rate to treat simple stenosis did not show any difference between BA and ST group, thus suggesting that tracheal dilation without prosthetic implantation should be the treatment of choice with this type of stenosis. Conversely, a very high relapse rate (>90% of cases) has been reported in complex tracheal stenosis treated with BA only, therefore indicating that stent placement may be the best solution in most of these cases (6). In our results, patient selection and timing of stent removal could have contributed to the high success rate in the treatment of complex stenosis in ST group. Notably, the exclusion of patients who required stent removal due to intolerance in the 12 months following endoscopic treatment certainly have influenced the study primary outcome among ST patients. However, data available in literature and clinical experience suggest that the long-term efficacy with stent placement can only be achieved when the prosthesis has remained in place for the necessary time (i.e., >1 year) to stabilize trachea. We concluded that ST seems to be more effective in achieving stabilization of tracheal patency in complex benign tracheal stenosis when compared with BA, although burdened with a significantly higher number of adverse effects. Finally, our data also showed that laser technique was less used in successfully treated patients of BA group than in ST, suggesting that in patients undergoing endoscopic dilatation the subsequent use of laser to obtain the excision of the scar area may be associated with relapse of stenosis. Also in the autoimmune stenosis group laser is associated with a risk of endoscopic treatment failure. In these cases, a cold knife approach avoiding laser is preferred, whereas stent positioning is advisable only in case of relapses. In conclusion, in patients with complex tracheal stenosis, the endoscopic therapy should be based on a multidisciplinary discussion considering the anatomical location of stenosis, the inflammatory state of the laryngeal-tracheal mucosa and the level of cartilage injury in order to choose the endoscopic approach technique with the best risk–benefit profile.

Upper Malignant Airway Diseases

Neoplastic pathologies can involve upper and lower airways not only as a primitive localization, but also following a metastatisation process. The development of Distant Metastasis (DM) represents an important prognostic factor. Identification of characteristics capable of predicting the risk of DM occurrence could allow patients stratification in order to optimize multi-modal management. The study confirmed that a significant number of patients with local sovra-glottic cancer may develop distal metastasis despite treatment during follow-up. The metastatic dissemination of upper malignant airway diseases significantly reduced survival, as confirmed by our COX regression analysis showing that who developed metastases has 3.5 times more risk of dying at 5-years in the overall population. For patients who did not have HPV infection, it does not seem that the development of metastases impacts on prognosis, probably because the pathology is locally aggressive. In patients who had HPV infection, instead, the presence of distal metastases significantly raises the mortality. Smoking status, advanced malignant disease at the time of diagnosis, and poor response to treatment were independent risk factors associated with the late event of metastases development. Moreover, our exploratory analysis concerning the difference in survival according to the sites of metastatisation shows that patients who developed lung metastases live longer. Lung metastases may be susceptible to radiotherapy, and this affects survival. In conclusion, the early phenotyping of patients at major risk of late metastasis onset could be a useful knowledge allowing patient stratification at the time of diagnosis, and consequently a therapy modulation with an intensification of the strategy treatment in those malignant diseases more likely associated with DM occurrence.

In conclusion, our results show that early bronchoscopy, when applied to locally advanced lesions causing CAO, improves prognosis for malignant airway disease; for benign airway diseases the endoscopic approach with stenting placement seems the best option in terms of clinical results; for malignant diseases of the upper airways, a combined treatment including surgery should be considered, even though the possibility of distal metastasis development is not excluded.

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