

Revisiting bronchoscopic intratumoral chemotherapy in malignant central airway obstruction via EUS-B approach and its review of literature

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Abstract

Critical central airway obstruction has always been a dreaded complication to which interventional pulmonologist commonly encounters. There have been various modalities which are used for the management and palliation, which includes mechanical coring, laser, cryoextraction, electrocautery and airway stenting. Rigid bronchoscopy with or without jet ventilation has been corner stone of therapeutics and palliation of central airway obstruction. There are only a few conditions where it is not possible to use rigid bronchoscopy. Here we report a case of metastatic tracheal tumour which presented with critical airway obstruction in a

patient who had atlantoaxial instability (AAI) due to rheumatoid arthritis. Here we used endobronchial ultrasound scope (EBUS) via esophageal route, *i.e.* EUS-B guided approach for sampling of the tracheal tumour, and intratumoral chemotherapy was instilled in multiple sessions, which resulted in shrinking of tumour, thus relieving the critical airway obstruction. This is the first report of using EUS-B approach for intratumoral chemotherapy for tracheal tumors. Bronchoscopic intratumoral chemotherapy therapy (BITC) in tracheal tumors is also one of the options but has not been explored much and there has been a dearth of literature for it.

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Introduction

Malignant central airway obstruction is usually managed by multidisciplinary approach involving tumour debulking, stent placement and palliative radiotherapy (RT). Rigid bronchoscopy has been main stay for this procedure [1]. There are few conditions where rigid bronchoscopy is contraindicated or may prove counterproductive. Atlantoaxial instability is one of such cases where any manipulation of cervical spine could result in spinal cord compression [2]. In such cases BITC may be attempted via flexible bronchoscope, EBUS or EUS-B approach. EUS-B approach *i.e.* using endobronchial ultrasound scope (EBUS) for oesophageal ultrasound which has been used time and again, has proven to be effective and with less side effects [3]. We used this approach in our case of malignant central airway obstruction thus not comprising the airway. Later this approach was improvised for first time in available literature for intratumoral chemotherapy.

Case Report

A 53-year-old female farmer, non-smoker but with history of biomass exposure presented with cough for 4 weeks. She was diagnosed 3 years back with atlantoaxial Instability (AAI) due to rheumatoid arthritis for which she was using a semi-rigid cervical collar and was taking mycophenolate mofetil. She had cough which used to get worsened on exertion and was accompanied by noisy breathing. Patient had breathlessness which progressed from grade II to grade III in the last 3 months. Spirometry showed fixed airway obstruction with flattening of inspiratory and expiratory limb of the flow volume curve on spirometry. Chest radiology showed possibility of tracheal mass which was later confirmed on computerized tomographic scan (CT scan). CT showed soft tissue endotracheal lesion of size 15.5x13.9x28.1 mm approximately 8.8 mm proximal to tracheal

bifurcation. Mass had a broad base and was arising from the right lateral and posterior wall encroaching 75% lumen resulting in critical airway obstruction. Lung window showed centrilobular and peri-bronchial nodules in bilateral lower lobes with tree in bud appearance with ground glass opacity suggestive of pneumonia (Figure 1).

Bronchoscopy revealed fleshy globular mass which had tortuous vessels over it and Karl Storz scope (C-MAC® FIVE S) with outer diameter 3.5 mm could just be negotiated. Biopsy was deferred due to anticipated haemorrhage as tumour appeared very vascular. As in cases of critical airway obstruction even mild haemorrhage can asphyxiate patient as airway is already being compromised. In addition, tracheal washings were positive for acid fast bacilli. Rigid bronchoscopy is the procedure of choice for managing central airway obstruction (CAO). However, in our case it was not possible due to AAI [3]. So, TBNA was planned *via* EUS-B approach. EBUS scope (EVIS EXERA II, Olympus Inc., Tokyo, Japan) was introduced *via* oesophagus [3,4]. Sonography showed heterogenous mass with a coursing vessel and had well defined margins. It was obliterating almost 75% of lumen and was extending almost 2 cm longitudinally. EUS-B guided FNAC was done and three passes were taken. FNAC was suggestive of squamous cell carcinoma. PET CT showed FDG avid very small subcarinal nodes (SUV 4.2) and mesenteric nodes (SUV 4.9) along with endotracheal mass (SUV 9.6) rendering it non-operable.

In non-operable critical airway obstruction, only options are related to palliation of symptoms. Palliation of symptoms can be achieved by debulking procedures *via* rigid bronchoscopy (RB) or by using radiotherapy. RB was not an option as the patient was having AAI. Radiotherapy primarily was deferred as acute oedema post RT would have resulted in a catastrophe in form of asphyxia.

Systemic chemotherapy alone would have taken long time to act and patient had tuberculosis which would have become fulminant. Thus, there was need of modality that could palliate symptoms and be acceptable. Hence, intratumoral chemotherapy therapy (ITC) for palliation of CAO was considered. After informed consent, she underwent novel EUS-B guided intratumoral cisplatin instillation. Using EUS-B had advantages as critically obstructed airway was not compromised further. ITC required multiple sessions and with this approach complications such as hypoxia, aspiration pneumonia, haemorrhage and fever, which have all been seen in previous studies (Table 1), were avoided. Patient needed systemic chemotherapy as it was a metastatic disease which was started after 4 weeks of initiation of antitubercular treatment.

For EUS-B guided ITC, EBUS scope was introduced in oesophagus. After visualizing endotracheal mass *via* EUS-B, EBUS needle was used to puncture it and in first session 10 ml of cisplatin in aqueous solution (4 mg/ml) was instilled into the mass in three different sites. Dose was according to previous study where they have used cisplatin intratumorally [3]. Minimal increase in size was visualised sonographically while instillation. Patient had no peri procedural and post procedural complication and check bronchoscopy after 1 week showed around 10% decrease in size. Sessions of ITC were repeated at week 2, 3 and 4. In the 3rd and 4th week we used cisplatin 40 mg (4 mg/ml) in combination with gemcitabine 500 mg (100 mg/ml) as mass had shrunk in size and there was scope of instilling more volume of drug. After 4 weeks of anti-tubercular treatment patient was started on systemic chemotherapy. There was almost 50% reduction at 4th week. Check FOB after 6 months showed that CAO reduced to almost 25 % (Figure 2). Follow-up CT scan was planned but could not be done as patient expired due to sudden cardiac arrest, a year after the initial procedure.

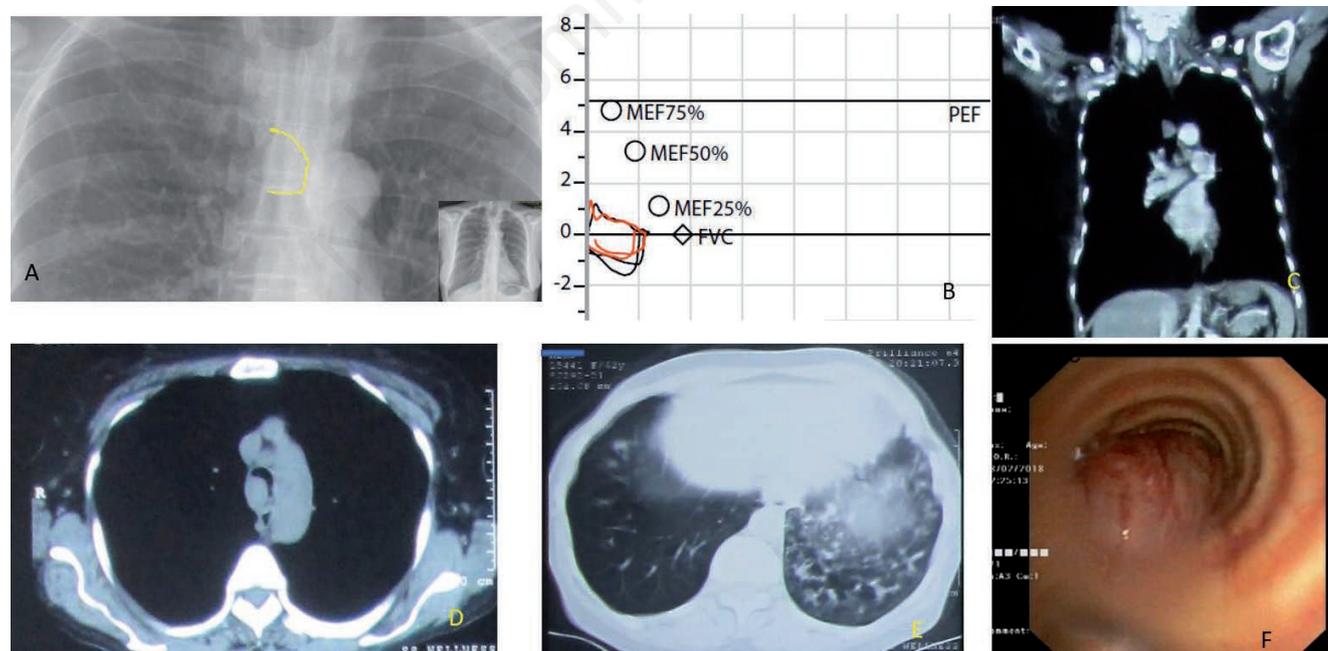


Figure 1. a) Zoom out image of chest radiograph showing tracheal mass (marked in yellow outline) arising from right tracheal wall occluding the lumen. b) Spirometry showing flattening of expiratory limb suggestive of intrathoracic obstruction. c) Coronal section of chest tomogram showing tracheal mass in lower one third of trachea d) Axial section showing tracheal mass causing more than 70% obstruction. e) Lung window showing tree-in-bud appearance and GGO. f) Bronchoscopic image showing tracheal mass causing almost complete obstruction of the tracheal lumen.

Discussion

Intratumoral chemotherapy was first used by Bateman *et al.* in 1958 where it was used in breast carcinoma with 66% improvement rate. It has been used over the years for lid carcinoma, head and neck carcinoma, skin carcinoma and deep seated intra-abdominal tumour with variable success [4].

BITC has been used in past in lung cancer but has not gain

much popularity. Following table summarizes systematic review of ITC in lung cancer, where extensive literature search was done, resulted in 24 studies out of which 13 results were excluded as 4 were not in English, 4 were reports about metastasis of lung tumours in different parts of body and were not about intra-lesional chemotherapy, 3 were intertumoral chemotherapy during thoracic surgery while other 3 were review articles (Table 1).

BITC appears to be effective modality in non-emergent central airway obstruction for palliation. It results in higher concentration

Table 1. Systematic review of bronchoscopic intratumoral chemotherapy (BITC).

S No	Author (year)	Clinical presentation	Protocol	Response	Complication
1	Matthay <i>et al.</i> [6] (1986)	Potentially resectable non-small cell carcinoma of the lung	ICT using flexible fine needle through the bronchoscope. Peripherally located lesions, not visible through it, were entered with fluoroscopic guidance. Agent used BCG	No response. Not lengthen disease-free interval or prolong survival in patients with non-small cell lung cancer	Malaise fever
2	Celikoglu <i>et al.</i> [7] (1997)	93 patients with endobronchial obstruction	1-3 ml each of 50 mg/ml 5-fluorouracil, 1 mg/ml mitomycin, 5 mg/ml methotrexate, 10 mg/ml bleomycin and 2 mg/ml mitoxantrone. In each session bronchoscopically with direct intratumoral injection was performed with a flexible needle	81 of the 93 patients. Endoscopically visible tumours were reduced in size, and infiltrative changes were also improved	8 patients had febrile episodes
3	Weill <i>et al.</i> [8] (2000)	12 patients with endobronchial mass (6 adenocarcinomas 6 squamous cell ca) All patients' tumour contained a p53 gene mutation	Adp53 (dose range, 1 x 10 ⁽⁶⁾ to 1 x 10 ⁽¹¹⁾ plaque-forming units) was administered by bronchoscopic intratumoral injection once every 28 days.	Six of the 12 patients had significant improvement in airway obstruction, and 3 patients met the criteria for partial response	No complications
4	Celikoglu <i>et al.</i> [4] (2006)	17 patients of NSCLC preoperatively	Direct injection of a maximum dose of 40 mg cisplatin in aqueous solution (4 mg/ml) into the tumour through a flexible bronchoscope; administered four times: once a week during a 3-week period necrotic tumour debris was removed by piecemeal resection with forceps and suction at each session		No major complications
5	Fujiwara <i>et al.</i> [9] (2006)	15 patients	Ad5CMV-p53 (ADVEXIN) was injected directly into the primary tumour, either endobronchially using a bronchoscope or percutaneously under computed tomography (CT) guidance	1 patient had a partial response (squamous cell carcinoma at the carina), 10 patients had stable disease, with three lasting at least 9 months, and two patients had progressive disease	Transient fever
6	Jabbardarjani <i>et al.</i> [10] (2007)	100 patients with unresectable lung cancer and endobronchial lesion	20 ml cisplatin with the concentration of 50 mg/100 ml was injected into the bulk of the tumour through the special needle. The procedure was performed weekly for 4 sessions	The lumen was considerably opened (more than 25%) in 80 patients	Bleeding (9), hypoxia (12), tachycardia (35), hypertensive crisis (3), and pain (27)

To be continued on next page

of chemotherapeutic agent in the tumour without or with very minimal systemic side effects. Conventional treatment using systemic chemotherapy and/or radiotherapy has proven unsatisfactory in yielding rapid restoration of airway patency in patients with malignant airway obstruction. Various successful palliative modalities use systemic treatment with combined local interventional modalities. In our case presence of tuberculosis delayed systemic chemotherapy but BITC can be used in such cases. After BITC, the concentration of anti-neoplastic agent decreases exponentially when it traverses through tumour vessels, and the drug concentration becomes half in 40 micrometres [15]. Intralymphnodal instillation of chemotherapy has been also shown useful in reducing tumour mass but it was not used as nodes were very small.

Our is the first case where EUS-B approach was used to instil chemotherapy. It had many advantages like patient's airway which was already compromised was not shared and throughout the procedure patient had no episode of hypoxia. As it was a vascular tumour there was anticipated danger of bleeding in airway leading to asphyxia. This danger was averted as tumour was approached *via* oesophagus. Few studies showed post procedural pneumonia after BITC because of aspiration of chemotherapeutic agent. It too was taken care of as puncture was made through oesophageal wall so any spill of chemotherapeutic agent in lungs was averted.

There are few limitations which are responsible for BITC not gaining much popularity, first there are no larger trials to determine

its efficacy and safety profile. BITC takes longer time to palliate CAO when compared to rigid bronchoscopic coring and thermal endobronchial ablative measures. Expertise and evidence have remained the major issue. Most interventional pulmonologist are not comfortable with multiple sessions and theoretical complications, though practically only few developed pneumonias and rarely one required hospitalization.

Conclusions

BITC can be considered as an alternative neoadjuvant therapy to mechanical or thermal debulking for palliative management of centrally obstructing tumours, where tumour mass is easily accessible by bronchoscope with opportunity for direct intralesional injection of chemotherapeutic agent. Mechanical debulking and thermal modalities often unreachable in distal tumours or may have contraindications; bronchoscopic intralesional chemotherapy could provide an advantage over these modalities in such cases. It is safe, simple, cost-effective procedure which exhibited neither systemic toxicity nor any significant complications in expert hands. It can be done *via* regular flexible bronchoscopy or EBUS scope. Though further studies are needed to confirm these findings.

Table 1. Continued from previous page.

S No	Author (year)	Clinical presentation	Protocol	Response	Complication
7	Hohenforst-Schmidt <i>et al.</i> [11] (2013)	Five patients' stage IIIa-IV, performance status 2 (PS2)	EBUS-needle [EBUS-transbronchial needle dosing (TBND)] is aiming at six passes per lymph node to optimize the permeation of the drug	More than a 50% reduction, for a massive tumour mass	1 atelectasis
8	Mehta <i>et al.</i> [12] (2015)	22 patients	40 mg of cisplatin mixed in 40 ml of 0.9% NaCl administered to endoscopically visible tumour tissue via a flexible 19-gauge. Wang needle Injections were made in a fan pattern to disperse the drug solution throughout the tumour	The majority of patients (15/21, 71.4%) responded to therapy, defined as greater than 50% relative reduction in obstruction from baseline	No complications
9	Mehta <i>et al.</i> [13] (2015)	36 patients of recurrence in lung cancer after receiving full dose external beam radiation therapy (EBRT)	EBUS guided intratumoral cisplatin	24/35 (69%) had complete or whereas 11/35 (31%) had stable or progressive disease (non-responders)	3 pneumonia
10	Li S-Y <i>et al.</i> [14] (2016)	Ninety patients with NSCLC-SAO	PTS/ethanol mixture was, using NA-1C-1 needle, intratumorally injected to lower quadrant of tumour's root (not endothelium), starting from tumour to adjacent tissues. Each injection covered 4-6 sites	PTS treatment resulted in a significant objective alleviation rate [chest CT: 59.1% (95%CI: 48.1%-69.5%), bronchoscopy: 48.9% (95%CI: 38.1%-59.8%) at day 7	No major complication
11	Li X <i>et al.</i> [15] (2017)	Chronic obstructive pulmonary disease (COPD) with extraluminal growth	Bronchoscopy with APC and EBUS guided intratumoral injection cisplatin (2.5 ml and 4 mg/ml) using NM-200L needle	Bronchoscopy showed that airway patency in the left upper lobe bronchus was re-established with, cryotherapy and EITC	No major complication

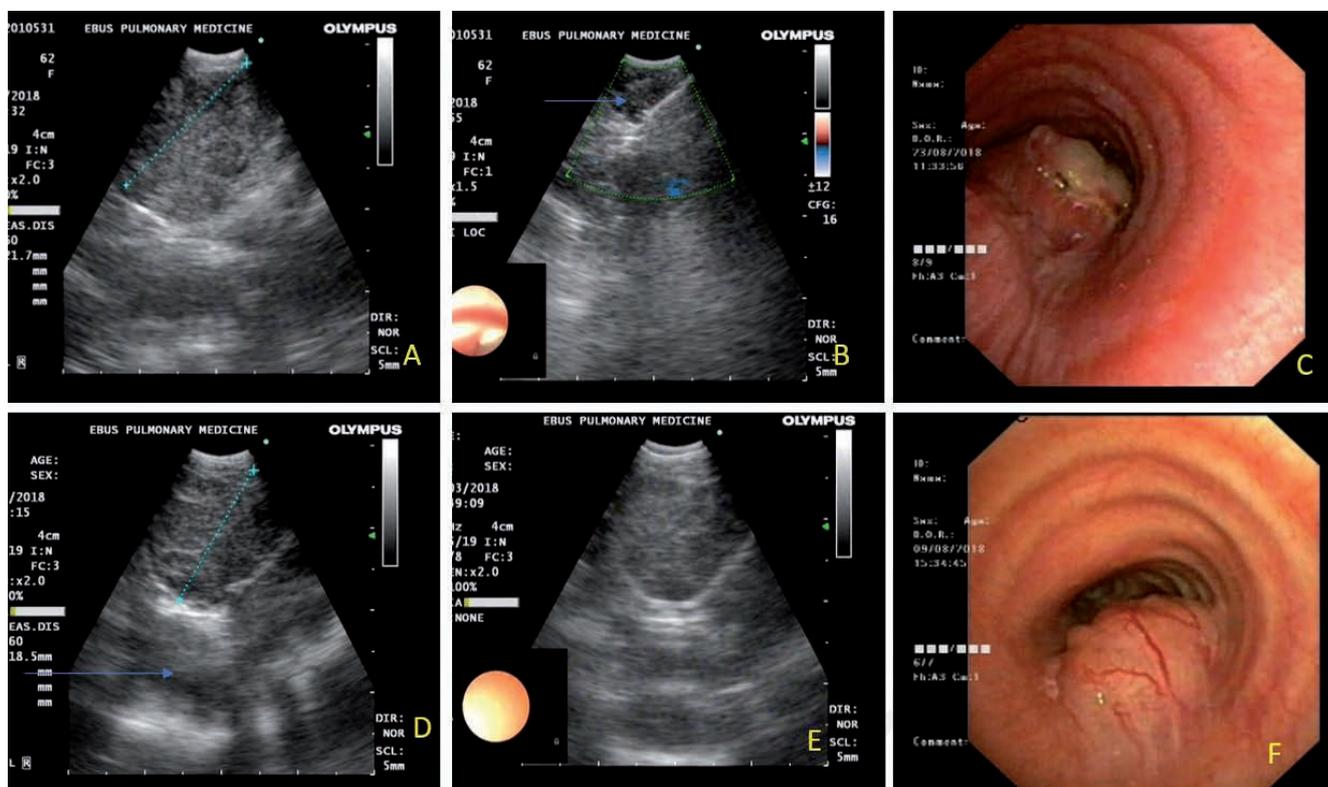


Figure 2. a) EUS-B image showing tracheal mass of size 22 mm. b) EUS image showing instillation of aqueous cisplatin (4 mg/ml), blue arrow showing pocket of cisplatin. Mass pierced at three places and in first session 10 ml, *i.e.* 40 mg cisplatin instilled intra lesionally c) Bronchoscopic image after 1st week showed shrinkage of mass with symptomatic relief. d) EUS-B image showed clear increase in airway indicated by blue arrow and decrease in size of mass. e) After 4th session mass shrunk further and airway cross-sectional area increased. f) Bronchoscopic image after 1 week of 4th session of intra lesional instillation.

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