

Favourable Prognosis when Lung-Cancer Patients with Superior Vena Cava Obstruction (SVCO) are Referred Promptly to EBUS-TBNA Prior to Medical or Surgical Management

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Abstract

Background

Primary care patients with superior vena cava obstruction (SVCO) syndrome are usually referred to emergency departments for urgent medical management (high-dose corticosteroids to reduce inflammation), pre-biopsy radiotherapy and/or stent placements to restore patency to the vessel. Biopsy, diagnosis and staging of the mediastinal mass is often postponed until resolution of SVCO symptoms. However, lung cancers metastasise rapidly and delays can influence the eventual outcome of patients. An additional merit in treating SVCO symptoms post-biopsy is that high-dose corticosteroids and pre-biopsy radiotherapy will degrade the quality of biopsy specimens, complicating diagnosis and subsequent management.

Aims

To determine if direct referrals of SVCO patients from primary care to the respiratory department for Endobronchial ultrasound (EBUS)-transbronchial needle-aspiration (TBNA) resulted in better outcomes.

Methods

Direct referrals to the respiratory department from primary care physicians were sought. A total of 8 patients with symptoms of SVCO were rapidly diagnosed via EBUS-TBNA and ROSE, radiotherapy and specific chemotherapy was initiated following communication with oncology colleagues. High-dose corticosteroids were administered post-EBUS.

Results

Rapid resolution of symptoms for SVCO were noted, without need for surgical intervention. In particular, one patient with small-cell lung cancer (the most aggressive type of lung cancer) remains well and cancer-free 14 months from diagnosis.

Discussion

EBUS-TBNA is a safe modality for biopsy in SVCO as there is no risk of further compression of the vessel. We need a paradigm shift in referral and a guideline of SVCO patients in primary care, an urgent biopsy is important in mediastinal cancers which have high metastatic potentials.

Keywords: EBUS-TBNA; ROSE; Superior Vena Cava Obstruction (SVCO) Syndrome; Prompt Biopsy; Mediastinal Cancer; Lung Cancer; Small Cell Lung Cancer; Stent

Abbreviations

EBUS: Endobronchial Ultra-Sound

TBNA: Trans-Bronchial Needle Aspiration

ROSE: Rapid On-Site Evaluation

CT: Computed Tomography

SVCO: Superior Vena Cava Obstruction

SVC: Superior Vena Cava

NHS : National Health System (the Health Care System in the UK Which is Free at the Point of Care to all Regardless of Race, Nationality, Gender or Creed)

Introduction

Any obstruction to the superior vena cava (SVC) can lead to a constellation of symptoms (see Table 1) known as the superior vena cava obstruction (SVCO) syndrome. Patients presenting with distended neck veins, facial plethora and other symptoms of superior vena cava obstruction (SVCO) syndrome in primary care are often referred to emergency services in hospitals for medical management of their symptoms (high dose corticosteroids to reduce inflammation), pre-biopsy radiotherapy and or stent-placement to restore patency to the superior vena cava (SVC).

Although SVCO can arise from a number of causes as listed in Table 1, often, the presentation of symptoms is the first indication of a mediastinal mass, usually confirmed by xray or computed tomography (CT) imaging at the patient's first visit to the hospital. Characterisation, diagnosis and staging of the mediastinal mass usually is postponed until SVCO symptoms are resolved. However, this adversely affects the prognosis since lung cancers have a rapid metastatic potential; the median survival of patients with advanced small cell lung-cancer without treatment initiation was 21.9 days [1]. In addition, patients with mediastinal malignancies presenting with SVCO have an overall poor prognosis [2].

Symptoms in SVCO	Physical Characteristics	Causes of SVCO (in decreasing order of incidence)
Chest pain Cough Disturbances with vision Dysphagia Dyspnoea Hoarse voice Nasal congestion Orthopnoea Pleural effusion Stridor	Coma Cyanosis Distended neck and chest veins Facial oedema Facial plethora Facial swelling Oedema in arms Papilloedema Stupor	Lung cancer Metastatic disease Lymphoma Thrombotic disease SVC in-stent thrombosis Benign causes

Table 1. Common symptoms, physical characteristics and causes of superior vena cava obstruction syndrome.

Invasive biopsy procedures in SVCO syndrome potentially risk further compression of the vein [3]. Current guidelines also recommend pre-biopsy radiotherapy for resolution of symptoms, however as the tumour cells are destroyed by the radiation, the quality of tissue samples collected for diagnosis are affected, making histological interpretation difficult [4].

This presents a very difficult conundrum since a biopsy sample is needed to enable diagnosis and to direct and plan subsequent therapeutic management. Percutaneous stent placement is often carried out as a palliative option to relieve symptoms in SVCO syndrome, [5] however delays in obtaining lung-tissue biopsies until resolution of symptoms increases the risk of tumour metastasis, thereby reducing the efficacy of future therapeutic protocols.

In partnership and close co-operation with our primary care physicians, we have had 8 direct referrals of patients with SVCO syndrome to our respiratory department via a fast-track chest-medicine clinic for EBUS services. We highlight the relevance of the speed of obtaining a diagnosis in ensuring a favourable outcome for our patients, especially where prompt initiation of treatment is crucial in lung cancers.

Methods

Study Design and Patient Enrolment

A convenience sample of 8 Patients with SVCO symptoms were enrolled upon direct referral from primary care for our EBUS services via our fast-track chest medicine clinic. Consent to the EBUS procedure was obtained by the consultant performing the procedure. Informed consent was obtained from these

patients to proceed with EBUS instead of waiting for measures to treat the SVCO symptoms first. This study, on evaluation of outcome on cancer prognosis where EBUS-TBNA was carried out with urgency prior to management for SVCO symptoms was registered as an audit at the Maidstone and Tunbridge Wells NHS Trust (audit reference number:256-1516). The study was carried out in accordance with Good Clinical Practice (GCP) guidelines [6]. All patients and subjects were treated appropriately with due care as per the requirements in the Declaration of Helsinki [7].

Pre-EBUS Checks and Procedure

X-ray and CT imaging of the chest was performed as a priority on patients presenting with SVCO. The anti-coagulation status was ascertained prior to the procedure; anti-coagulation medication was withheld from the time of admission to the time of procedure. Ideally, anti-coagulation was withheld 7 days prior to EBUS, where this was not possible, especially in emergency situations such as in SVCO syndrome, appropriate pre-cautionary steps were in place for hemostasis (ie. cold saline, topical sympathomimetics or balloon tamponade).

EBUS Procedure

EBUS-TBNA was conducted under conscious sedation, all patients were administered between 50-100 mg of fentanyl combined with low-dose (<3mg) midazolam intravenously. The amount of sedation given to each patient was titrated according to their levels of anxiety assessed using clinical judgement. 2% transtracheal lignocaine spray was administered just prior to advancing the bronchoscope and an additional 2% lignocaine was administered down the bronchoscope on visualisation of the vocal cords to anaesthetise the airways.

Doppler ultrasound was used to determine the area to be punctured, colour-flow Doppler was used to estimate the safe distance where the needle puncture-site was to be placed away from the SVC. Approximately 5 needle punctures were carried out at each site.

Rapid-on-Site Evaluation (Rose), Diagnosis and Management Planning

Biopsy samples were assessed by rapid on-site evaluation (ROSE) by a consultant histopathologist by fast H&E staining and microscopy in the procedure room prior to formal histopathological confirmation by our accredited laboratories. The diagnosis was conveyed to the multi-disciplinary team (MDT) meeting and treatment options were discussed and initiated immediately after.

Post-EBUS Management

Oral dexamethasone (16mg, single dose) was given immediately post-EBUS. Patients who experienced difficulty

in swallowing were administered Dexamethasone 16mg by continuous subcutaneous or continuous infusion (CSCI), or IV /24 hours.

Results

Eight patients with clinical symptoms of SVCO were urgently referred for EBUS services, urgent staging by CT was carried out and biopsy samples of the tumour was obtained by EBUS. All eight patients had large mediastinal masses which caused obstruction of the SVC (Table 2). All eight patients who had EBUS-TBNA urgently on presentation of SVCO symptoms survived during the period post-EBUS until resolution of the symptoms of SVCO.

Patient number 3 died 31 days following EBUS and following resolution of SVCO symptoms however this patient was too unwell to commence chemotherapy and succumbed to death from respiratory failure. Patient number 7 died 22 days following EBUS and after resolution of SVCO symptoms, however this patient was shown to have widespread metastasis to the liver and adrenals.

Three of the patients enrolled into the study are currently still alive post-resolution of SVCO symptom, one patient is still alive and symptom-free two years following initial presentation with symptoms since this patient went on to have chemotherapy and a lobectomy.

Discussion

Main Findings

The first patient in Table-2 was a 72 year old gentleman who presented to his family-doctor with new onset of dyspnoea, facial flushing and chest tightness on postural changes. A clinical diagnosis of SVCO syndrome was made at the primary-care level. The patient was referred immediately to our EBUS services via the lung-cancer pathway [8]. An urgent chest X-ray revealed a 5 x 6 cm right-sided mediastinal mass (see Figure 1) with no tracheal displacement.

This patient received a diagnosis of small-cell lung carcinoma (SCLC). SCLC is the most aggressive form of lung cancer and has a very high rate of metastasis, usually to the brain, liver and bone. Early diagnosis and tumour staging is crucial to improve the prognostic value of the disease. This patient remains cancer-free and well to this day more than a year from his first presentation to his primary care physician and the success of this is attributed to the prompt diagnosis and staging of the cancer followed by early initiation of chemotherapy to treat the tumour.

EBUS-TBNA was performed and smears of the lymph node revealed a pleomorphic population of smaller cells with a

ID	Gender	Alive?	Current age or age at death	Staging	Survival (days) post – EBUS	Cause of SVCO	Cause of death	Histological Diagnosis
1	M	Y	73	T2b N3 M0	still alive (1 year)	large right mediastinal mass of 5 x 6 cm extending to the right para-tracheal region	patient is still alive and is cancer-free	Small cell lung carcinoma
2	F	N	52	T4 N3 M1a	104	large 7 cm malignant mass in the right upper lobe invading the superior mediastinum.	Spinal metastasis following a period of remission post chemotherapy	Squamous cell carcinoma
3	M	N	78	T4 N0 M0	31	5 x 8 cm para-mediastinal mass, encasing the aorta and main right pulmonary artery.	Respiratory failure – patient was too unwell to continue chemotherapy following resolution of SVCO	Squamous cell carcinoma
4	M	N	68	T1b N3 M1b	163	Extensive mediastinal mass with positron emission tomography (PET) standard uptake values (SUVs) ranging from 9.9 at the right hilum to 8.8 in sub-aortic region.	Pancreatic metastasis	Small cell lung carcinoma
5	F	Y	51	T2a N2 M0	Still alive (2 years)	Multiple large mediastinal lymph gland enlargements and a spiculated right upper lobe mass extending to the right hilum.	Patient is still alive, following resolution of SVCO, neoadjuvant chemotherapy administered – had lobectomy and is well and symptom free.	Non-small cell lung carcinoma - Adenocarcinoma
6	M	N	66	T3 N3 M0	255	A large mediastinal mass of 7.8 cm extending to the right middle lobe	Mediastinal tumour recurrence and spread to digestive tract.	Non-small cell lung carcinoma – Adenocarcinoma
7	M	N	72	T4 N3 M1b	22	A 4.7 x 3.7 cm right upper lobe mass extending towards the mediastinum.	Wide-spread metastasis to liver and adrenals	Small cell lung carcinoma

8	M	Y	82	T4 N3 M1b	Still alive (1 year)	A large mediastinal mass of 9.0 x 5.0 X 4.8 cm, also encasing the right main bronchus.	Patient is still alive, following resolution of SVCO however is currently undergoing palliative chemother- apy.	Non-small cell lung carcinoma -- Adenocarci- noma
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Table 2. Demographics, survival time, histological diagnosis and cause of death of the patients enrolled into this study.

low nuclear to cytoplasmic ratio and prominent nucleoli with bizarre shapes, mitoses and multi-nucleation (see Figure 2). ROSE carried out in the EBUS suite by the consultant histopathologist delivered a preliminary diagnosis of small-cell carcinoma which was later confirmed by detailed analysis from the laboratories.

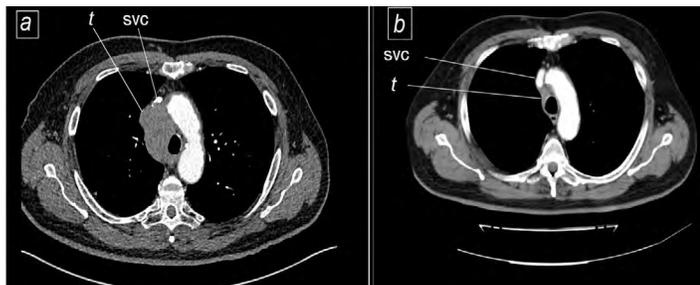


Figure 1. CT-images showing mediastinal bronchogenic tumour causing SVCS and its resolution following chemotherapy. (a) A large 5 x 6 cm mediastinal mass (t) in the right paratracheal region is noted on CT imaging, compressing on the superior vena cava (svc). (b) following diagnosis and staging by EBUS-TBNA and ROSE, appropriate management of the tumour and chemotherapeutic regimens were initiated, resulting in significant tumour regression two months later and cessation of symptoms.

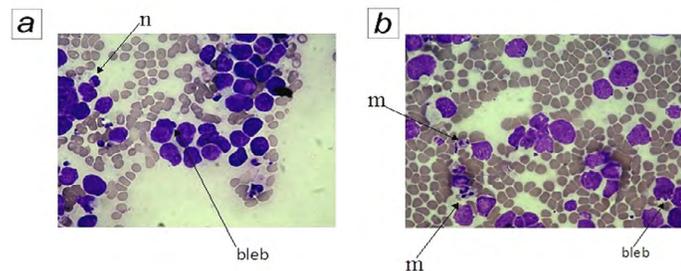


Figure 2. Transbronchial needle-aspirate (TBNA) of lymph node samples of patient A showing features of small cell carcinoma. (a) The cells typically have a small cell-size, finely granular nuclear chromatin, scant cytoplasm. Some cells have large bizarre nuclei (n) and some cells also show blebbing of the cell-membrane (bleb) (b) frequent mitotic stages (m) are also seen, here cells are shown in typical anaphase

stage where the chromatin are drawn to opposite poles just prior to cell-division. Also seen are some cells with characteristic blebbing (irregular protuberances) of the cell-membrane.

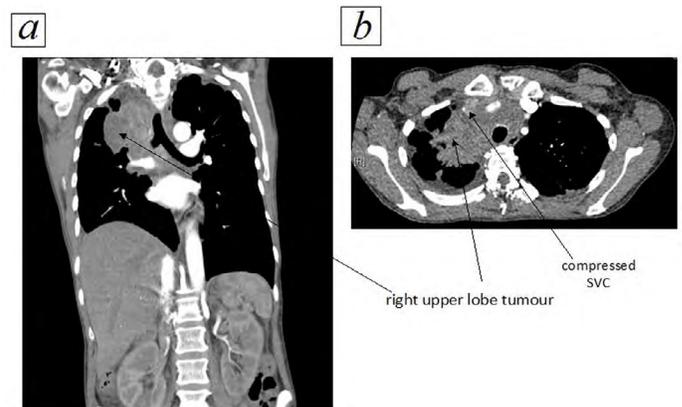


Figure 3. CT scans of a patient with a large right upper lobe tumour showing SVCS. (a) A sagittal CT image view showing the thorax and abdomen. A large 7 cm malignant mass is seen in the right upper lobe invading the superior mediastinum. (b) all the vessels are grossly displaced and effaced, especially the superior vena cava (arrowed), however the vein is marginally patent and not completely occluded. We also noted a right-paratracheal node (not seen in the images here) measuring 37 mm and a hilar node measuring 22 mm. There was also a small degree of pleural effusion on the right, seen in (b). There was no evidence of any hepatic, adrenal or para-aortic metastases.

Figure 3 shows the CT imaging of a female patient with a mass in the right-upper lobe, invading the superior mediastinum and encompassing the superior vena cava. She was a smoker, presented at her family doctor's surgery with symptoms of shortness of breath, unintentional weight loss, throat tightness and difficulty in swallowing. The patient did not have any co-morbidity, however there was a strong family history of cancers; hence she was urgently referred via the two week rule, [9] to our department. On examination we found evidence of left arm swelling, distended neck veins and facial plethora, strongly suggesting a clinical diagnosis of SVCO syndrome.

EBUS-TBNA on this patient was uneventful, and adequate samples were harvested. Although this patient had a significant degree of SVC-compression (Figure 4), harvesting the cells within the tumour mass did not contribute further compression of the vein and its tributaries. Sampling of the tumour mass by EBUS and ROSE subsequently confirmed poorly differentiated squamous cell carcinoma.

The patient underwent rapid specific chemotherapy for her cancer and showed encouraging signs of resolution of the tumour and resolution of the symptoms of SVCO. She later succumbed to metastasis of the tumour to her spine but importantly, this occurred 104 days post-EBUS procedure.

Prior to this study, patients with symptoms of SVCO presenting in primary care would be rapidly referred to emergency services in hospitals for appropriate management and/or percutaneous stent deployment. While this manages a very important oncological emergency, the diagnosis and staging of lung cancers is postponed till a later date, risking the chance of metastatic spread of the mediastinal tumour.

The approximate procedural time taken to obtain a biopsy sample by EBUS is 30-45 minutes, after this, patients would be able to receive high-dose corticosteroids and radiotherapy to relieve the pressure surrounding the SVC. During the EBUS procedure, patients are under the care of highly trained theatre staff and the procedure takes a relatively minimal amount of time, not adversely affecting the outcome on patients.

The patients whom we obtained biopsy samples from did not require percutaneous stent placement later, since the cancer was treated promptly by specific chemotherapy, this relieved the tumour load and pressure on the SVC.

The biopsy samples of patients with SVCO subjected first to EBUS-TBNA were of much better quality, compared to if the patients had been pre-treated with steroids or radiation. Steroids and radiation are known to degrade the quality of the biopsy samples, complicating diagnosis [4,10].

There are number of causes that can result in obstruction of the superior vena cava, one of them being a thrombotic occlusion of the vein. Thus an additional advantage of performing EBUS first in SVCO syndrome is that the ultrasound modality in EBUS is a very good method in viewing a thrombus within the vessel [11].

Strengths and Limitations of this Study

This was a small observational study (using a convenience sample), to evaluate if a better outcome would be reached if patients with SVCO syndrome presenting initially to their primary care physicians were referred directly to EBUS-TBNA rather than delaying the process of biopsy and staging until

resolution of the symptoms. The rationale behind this study was that speed in procuring an accurate diagnosis is crucial in lung-cancers and often, the presentation of SVCO symptoms in primary care can be the first instance where a cancer is first diagnosed.

The strength of a small-sized observational study is that such studies would be quick to implement, easy to review patient notes and follow-up of patients would be more thorough as more time can be spent for individual patient contact. However, since this was a small study to test a concept where direct referrals would have a better outcome due to the speed of eventual implementation of therapeutic protocols following diagnosis, a larger confirmatory study is needed.

On the administrative side, obtaining institutional approval is easier for smaller-sized and especially single-centre studies. Fewer resources are needed in a small-scale study such as this and less staffing costs are involved.

In studies of this nature where a change in the referral process or in the clinical management of patients with SVCO is sought, the outcome or "end-point" measure would be either an increase in survival or the increase or decrease in mortality rates. This study clearly showed that subjecting a patient to EBUS first and treating the symptoms of SVCO later did not have any adverse effect on their clinical outcome. This was because, the biopsy procedure only took approximately 30 – 45 minutes with a well-trained team in attendance, the medical treatment and initiation of radiotherapy was promptly delivered post-EBUS.

The main limitation was the number of patients enrolled and followed up in this study. We propose to address this in due course once funding arrangements are in place. Small studies are prone to over-estimate the results of an observation hence giving rise to false-positive results. Although this study shows encouraging results where the symptoms of SVCO were effectively managed post-EBUS and that an efficient biopsy sample was obtained, facilitating rapid diagnosis and starting of chemotherapy, we hope that a larger study would confirm our current findings.

The patients included in this study had stages 1-3 of SVCO using the classification of Yu and colleagues [12], thus they could be safely biopsied using EBUS-TBNA. Our patients were treated with high dose corticosteroids post-EBUS and post-biopsy radiotherapy was initiated with the co-operation of our colleagues in oncology. One limitation is that patients with stage-4 SVCO symptoms (significant cerebral oedema, confusion, obtundation, laryngeal oedema, haemodynamic compromise, syncope and renal failure) would have to undergo immediate interventional measures as well as stent deployment to restore patency to the SVC. These patients would naturally require a period of post-operative convalescence prior to undergoing any interventions for obtaining a biopsy.

Interpretation of Findings in Relation to Previously Published Work

The superior vena cava (SVC), a large vein formed by a merger of the brachiocephalic and azygous veins, it is approximately 6-8 cm in length and 1.5-2cm in diameter. The vein is very thin walled and therefore any obstruction due to thrombosis within the tributaries of the SVC or from external compressive forces from a malignant or non-malignant mass can exert tremendous pressure on the vein and thereby occlude it. The occlusion causes a spectrum of clinical symptoms known as the "superior vena cava obstruction (SVCO) syndrome", a potentially life-threatening oncological emergency where outflow from structures in the head, neck, and most importantly the brain is impeded, thereby raising the intracranial pressure.

Thus, any invasive surgical techniques which impose further compression of the vein and its tributaries can increase the mortality and morbidity risks. Percutaneous stenting of the SVC is now considered a routine procedure albeit with a significant but acceptable morbidity [13]. In contrast, the EBUS method of obtaining biopsy samples of the mediastinum occurs via the trachea, a collagen-strengthened natural tube through which the advancement of the biopsy-needle-probe does not cause any displacement or further compression of the SVC, and thus is considered safe.

We chose to carry out EBUS-TBNA on our patients for four reasons; sonographic visualisation of the mass, cytological sampling, sonographic assessment of the extent of the obstruction in SVCO and possible staging in the event of a diagnosis of a primary lung carcinoma.

In our EBUS suite, we frequently combine the sampling of lung-masses with ROSE of smears [14], this process requires the presence of a qualified histopathologist in the endoscopy-theatre setting, ready to assess, diagnose and triage the newly-harvested specimen and to facilitate a clinical opinion on the prognosis and subsequent therapeutic options and studies that may benefit the patient.

Dexamethasone is known to reduce swelling, although the patho-physiology of this process is not clearly understood. Its role in SVCO symptom-management is to reduce the pressure of the tumour surrounding the SVC. However, our patients were given corticosteroids post-EBUS, since corticosteroids given during the pre-biopsy period have been previously reported to degrade the quality of the tissue samples, complicating histopathological analysis [10]. Pre-biopsy radiotherapy is also usually given to shrink the tumour surrounding the SVC, however we chose not to administer this pre-EBUS since it is also known to affect the quality of biopsy samples and therefore making histological interpretation a very challenging effort [4]. Thus, the management options for SVCO syndrome would

complicate the eventual diagnostic process for characterisation of the tumour. However, if EBUS-TBNA is performed urgently without delay, then a diagnosis could be obtained and the symptomatic treatment of SVCO can then take place post-EBUS. The speed of diagnosis facilitated by EBUS-TBNA followed crucially by ROSE, which helped to deliver a preliminary diagnosis which we could communicate to our colleagues in oncology, helped to hasten the initiation of chemotherapy in patients with SVCO.

A previous study by Yu et al. have suggested, that if the clinical symptoms are not life-threatening then the ultimate outcome of patients with SVCO syndrome could be improved if the underlying tumour is dealt with in a timely fashion [12]. They propose that patients with stage-1, 2 and 3 SVCO symptoms should undergo staging and urgent management of the underlying tumour. The authors of that study also question the value of stenting in aggressive tumours such as small-cell lung cancer, where obtaining a diagnostic sample is of primary importance [12].

Implications for Future Research, Policy and Practice

The close-relationship that our respiratory department has with our local primary care physicians was crucial to the success in carrying out this observational study. The referral process that we have sought from primary care needs to be emulated in a wider scale among other trusts that provide EBUS-TBNA service.

We propose therefore that patients with SVCO presenting in primary care should be referred as a matter of urgency to centres that provide EBUS-TBNA for the rapid diagnosis and staging of the cancer. Prompt and rapid initiation of specific chemotherapy and radiotherapy following diagnosis of the tumour can result in rapid resolution of the symptoms of SVCO without the need for invasive procedures.

We reiterate that pre-biopsy radiotherapy and corticosteroid therapy be withheld until after EBUS-TBNA to preserve the quality of the biopsy samples.

Conclusions

In conclusion, we emphasise that it is safe to carry out EBUS-TBNA in patients with stage 1-3 classified SVCO prior to medical management of symptoms and radiotherapy to reduce the swelling surrounding the SVC. In addition, treatment of SVCO symptoms post-EBUS is advantageous since the quality of biopsy samples would be preserved and not degraded following high corticosteroid doses and/or radiotherapy. We encourage trusts that provide EBUS-TBNA as a service to seek better co-operation with their primary care trusts and to educate the general medical community on the advantages of

carrying out EBUS first in SVCO syndrome.

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Conflict of Interest

The authors declare that there is no conflict of interest whatsoever.

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Author Contributions

LGD – assisted SAH at the EBUS sessions, examined and provided post-procedure care for patients, reviewed CT images, prepared and analysed biopsy samples by microscopy, carried out audit and analysed results and wrote the manuscript

BY – provided histopathology support and analysis of the biopsy samples (EBUS-ROSE) during the EBUS sessions and reviewed the manuscript.

AFL – reviewed the manuscript and provided advice on the study design

SAH – was the consultant at the EBUS sessions, providing clinical care and after-care to the patients, was mentor and clinical supervisor to LGD and reviewed the manuscript

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