

Benign Endobronchial Neoplasms: A Review

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Abstract

Benign endobronchial neoplasms are rare tumors of the tracheobronchial airways. These neoplasms are mostly slow growing and usual presentation is related to bronchial obstruction. Most patients present with symptoms such as, wheezing, cough, chest discomfort, hemoptysis or recurrent pneumonias. Radiographic findings may demonstrate, endobronchial lesions, atelectasis, pneumonia, bronchiectasis and in some instances even mediastinal shift. Imaging modalities are often non-specific. These lesions can lead to complications stemming from obstruction or asphyxiation, massive hemoptysis; requiring urgent surgical management. It is imperative to recognize their presence in a timely manner so that the appropriate intervention may be instituted. The reemergence of rigid bronchoscopy has bolstered the armamentarium of pulmonologists in diagnosis and management of such lesions. We review the clinical characteristics, diagnostic modalities and latest advancement in treatments and outcomes of benign endobronchial tumors.

Keywords: Endobronchial neoplasm; Benign; Airway obstruction

Introduction

Benign endobronchial neoplasms are rare tumors of the tracheobronchial airways. These neoplasms are mostly slow growing and usual presentation is related to bronchial obstruction. Most patients present with symptoms such as, wheezing, cough, chest discomfort, hemoptysis or recurrent pneumonias. Radiographic findings may demonstrate, endobronchial lesions, atelectasis, pneumonia, bronchiectasis and in some instances even mediastinal shift. Imaging modalities are often non-specific. These lesions can lead to complications stemming from obstruction or asphyxiation, massive hemoptysis; requiring urgent surgical management. It is imperative to recognize their presence in a timely manner so that the appropriate intervention may be instituted. The reemergence of rigid bronchoscopy has bolstered the armamentarium of pulmonologists in diagnosis and management of such lesions. We review the clinical characteristics, diagnostic modalities and latest advancement in treatments and outcomes of benign endobronchial tumors.

Classification

Benign endobronchial neoplasms are divided based on origin, into mesenchymal, submucosal glandular, and surface epithelial (papillomas) tumors [1]. The tumors of mesenchymal origin form the majority of these tumors, the most common being a hamartoma [2,3]. The classification of these neoplasms is listed in Table 1.

Hamartomas

Endobronchial Hamartomas (EH) are malformations caused by bronchial wall mesenchymal elements. They are the most common type of benign endobronchial neoplasms. Hamartomas occur more common in older males (ratio, 2-4:1) with the peak in the sixth decade [1]. It has been reported that factors like inflammatory lung disease and smoking contribute to a hamartoma [4]. Hamartomas contain a mixture of cartilage, bone, fat and smooth muscle tissues [5]. EH tend to have a higher content of fat than intraparenchymal lung hamartomas [6]. These EH are lined by respiratory epithelium. The ultrastructure of this epithelium contains a mixture of ciliated respiratory cells, clara cells, mucin secreting cells and type 2 pneumocytes. The stromal cells represent primitive mesenchymal cells and the cartilage demonstrates chondrocytes [1]. They usually to present with symptoms of bronchial obstruction like cough, wheezing, hemoptysis, dyspnea and fever [5].

Sequelae of endobronchial obstruction are easily evident on imaging; these include atelectasis, pneumonia and bronchiectasis. Sometimes the high fat content of the lesion is high enough to be evident on a computer tomography (CT) scan. Bronchoscopic examination shows a polypoid or pedunculated neoplasm, which is well circumscribed with a smooth and yellowish surface. The tumors do not involve the sub-mucosa [7]. An endoscopic biopsy is essential for definite diagnosis.

Our experience

Case 1: Symptomatic Patient with Airway Occlusion

An 85-year-old African American male presented with shortness of breath to the emergency department. His Chest radiograph (CXR) showed left lower lobe (LLL) opacity. Patient was started on intravenous

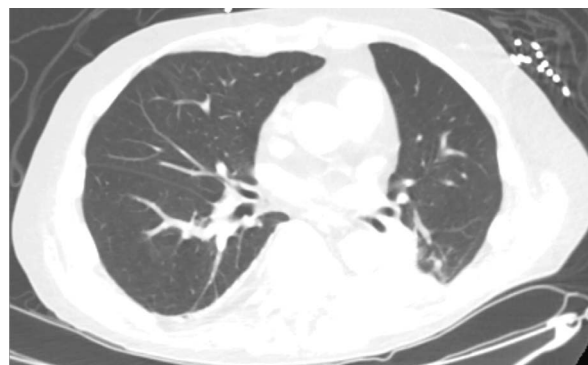


Figure 1: A sudden cutoff left lower lobe and distal atelectasis.

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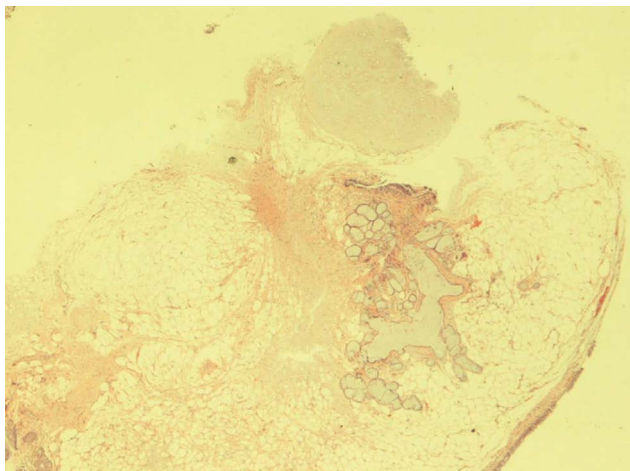


Figure 2: 5 mm well-circumscribed nodule composed of cartilage, adipose tissue, mucus glands and lined by ciliated respiratory epithelium. Consistent with endobronchial hamartoma. Which unlike peripheral hamartomas have mote adipose tissue.

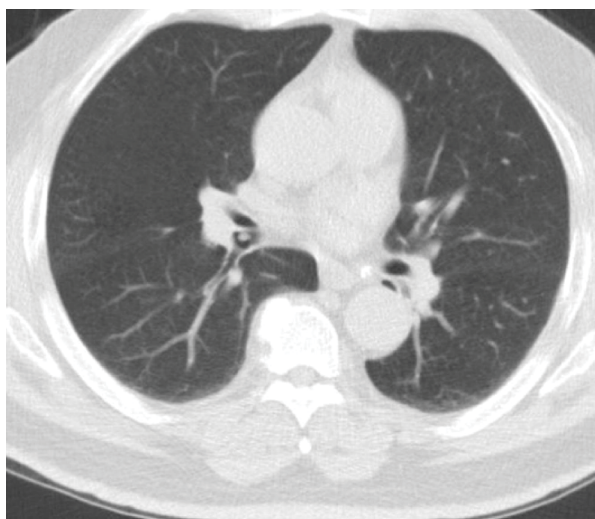


Figure 3: Possible pedunculated lesion in the distal right lung airway.

(IV) antibiotics to cover for possible health care associated pneumonia (HCAP). A CT chest done to evaluate the radiographic abnormality, demonstrated dense LLL atelectasis with a sudden cutoff at the lower lobe bronchus. (Figure 1) Patient underwent bronchoscopy that showed an endobronchial lesion with complete occlusion to the posterior sub-segment of the lower lobe. This was removed in toto by biopsy forceps. Pathology showed mature sub-endobronchial adipose tissue, cartilage, and mucous glands, suggestive of hamartoma. (Figure 2) The patient later succumbed to severe sepsis stemming from ischemic colitis during the same admission.

Case 2: Incidental Presentation

A 63 y/o African American male had a low-dose lung cancer screening CT that demonstrated an endobronchial lesion at the take off at the distal bronchus intermedius (Figure 3). Flexible bronchoscopy confirmed the presence of the endobronchial lesion (Figure 4a). An

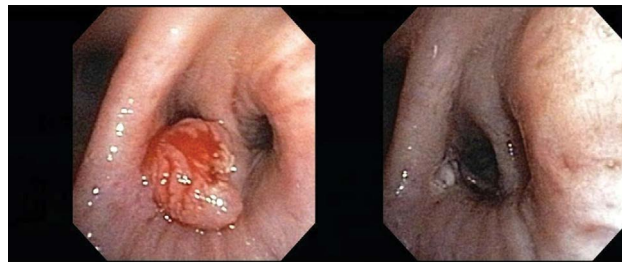


Figure 4: (a) Polypoid lesion in the distal bronchus intermedius, mid hemorrhage from a forcep biopsy, (b) the same lesion after snare electrocautery, base well cauterized.

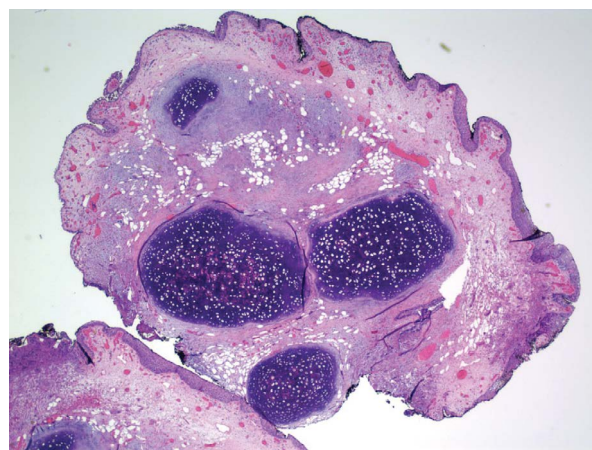


Figure 5: Lesion composed of cartilage and adipose tissue. Suggestive of endobronchial hamartoma.



Figure 6: Large right hilar lesion with both parenchymal and endobronchial components.

electro-cautery snare was used to excise the nodule (Figure 4b). The pathology demonstrated findings suggestive of a hamartoma (Figure 5). The patient is stable and has no new endobronchial lesions at 12 months.

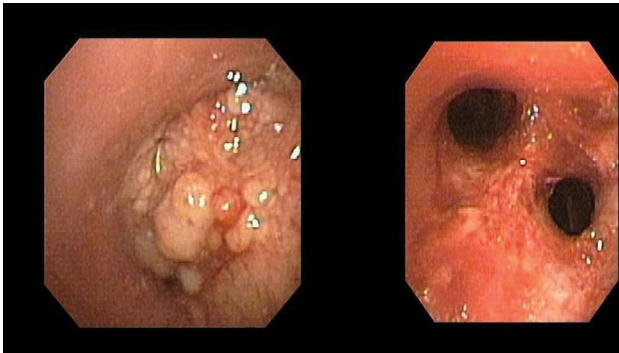


Figure 7: (a) right main bronchus almost completely occluded by an endobronchial lesion. (b) Right main bronchus reclaimed after tumor debulking.

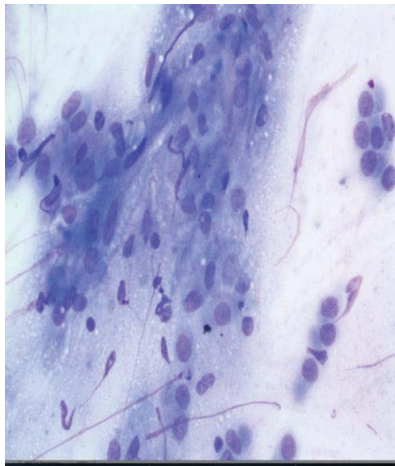


Figure 8a: Diff Quik stained slides show histiocyte-like cells forming syncytial aggregates. The tumor cells contain a granular cytoplasm and bland nuclei with inconspicuous nucleoli. (Diff Quik, 400x magnification)

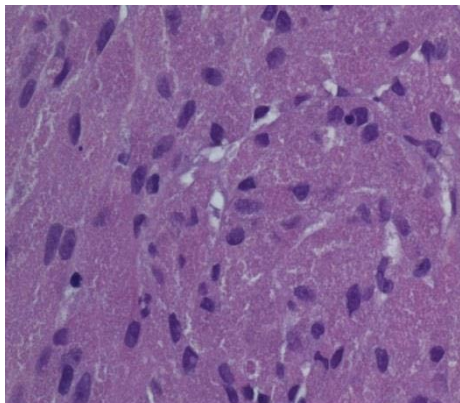


Figure 8b: The biopsy shows a syncytium of cells with granular cytoplasm and bland nuclei. No cytologic atypia, mitoses or necrosis is present. (H&E stain, 600x magnification)

Lipomas

Endobronchial Lipoma (EL) is an extremely rare benign neoplasm

Tumors of Mesenchymal Origin	Tumors of Submucosal Gland Origin	Tumors of Surface Epithelial Origin.
<ul style="list-style-type: none">– Hamartomas– Lipomas– Chondromas– Primary pulmonary leiomyomas– Granular cell tumors– Neurogenic tumors	<ul style="list-style-type: none">– Mucous Gland Adenoma– Pleomorphic Adenoma	<ul style="list-style-type: none">– Squamous papillomas<ul style="list-style-type: none">a) Solitaryb) Recurrent Papillomas– Glandular cell papillomas– Mixed Papillomas– Fibroepithelial polyps

Table 1: Classification of Benign Endobronchial Tumors [1].

of the lung with an incidence reported to range from 0.1% to 0.5% of all lung tumors [8]. Most EL arise from the sub-mucosal layer of the bronchus. Smoking and obesity are considered risk factors for EL [9]. Occur more commonly in males and at any age [10]. Histologically, lipomas are mostly a composite of mature adipose tissue and blood vessels. Myxoid change and spindle cell foci along with other mesenchymal elements can be present sporadically [11]. The surface is lined with columnar respiratory or metaplastic squamous epithelium. Due to the insidious presentation these patients are frequently misdiagnosed and treated as asthma [12]. There have been no reports of malignant transformation of lipomas. A CT imaging the tumor is composed of adipose tissue and shows no enhancement with intravenous contrast [13]. On bronchoscopic examination, this neoplasm appears as a soft, white, yellow or grey pedunculated mass. These lesions are not vascular and can be sometimes wide based [13]. An endoscopic biopsy is essential for diagnosis. However, the existence of a fibrous, firm sheath around the tumor can prevent adequate tissue sampling in 50% of the cases [15].

Chondromas

Endobronchial Chondroma (EC) is also extremely rare. These tumors have historically been misclassified as hamartomas [16]. Although, they are more common in the trachea, they can be found anywhere in the airway [17]. More common in middle aged (3rd to 5th decades of life) males [18]. Histology shows lesions composed of cartilage and lack of entrapped epithelium. Bronchoscopy shows a pedunculated, vascularized, pink tumor with a lobulated gritty surface. Hamartomas and chondromas are considered to be on the spectrum of benign mesenchymal lung neoplasms.

Primary Endobronchial Leiomyomas

Primary Endobronchial Leiomyomas (EL) account for approximately 0.66% of all benign lung neoplasms [19]. They are thought to arise from the smooth muscles of the bronchial tree. Origin from the areas of cicatricial fibrosis has also been proposed. The mean age of patients with primary EL is thought to be 30-40 years and has equal incidence for either gender. Some literature reports female predominance, however this is could be due to the over reporting of benign metastasizing uterine leiomyomas [20]. Histologically, the spindle cells are arranged in intersecting fascicles and whorls with tapered cigar shaped nuclei with bland chromatin and cytoplasm. The ultrastructure is similar to uterine leiomyomas. It is thus essential to distinguish EL from benign metastasizing uterine leiomyomas and leiomyosarcomas in women. As it is difficult to diagnose EL on routine imaging, a bronchoscopy is used to visualize and biopsy the neoplasm.

Endobronchial Granular Cell Tumors

Endobronchial Granular Cell Tumors (EGCTs) are very rare

benign pulmonary tumors. GCTs more commonly occur in skin and subcutaneous tissue, only 6-10% cases occur in the lung [21]. Less than 80 cases of pulmonary GCTs have been described in the literature since the first case of EGCT was described in 1938 [22]. It usually occurs in middle-aged individuals but cases have reported in children as young as 5 years old [23]. There is no gender predilection. African Americans have a higher propensity to develop the tumor [24]. Smoking may be an inducing factor but causality has not been confirmed due to the small number of reported cases [25]. The origin of granular cell tumors has been in debate since it was first reported. Abrikossoff believed these tumors originated from the skeletal muscle as they were initially reported originating from tongue, lips and muscles of lower extremities [27]. Thus EGCT's were traditionally called 'granular cell myoblastoma'. However, based on the electron microscopy findings and cytochemical studies, EGCTs are now believed to originate from Schwann Cells (neural cell) [27]. EGCT is characterized by submucosal infiltrate of round to oval tumor cells with eosinophilic granular cytoplasm. Tumor cells can often infiltrate into peribronchial tissue. Squamous metaplasia of overlying epithelium can be seen along with subepithelial basement membrane thickening [28]. Immunohistochemistry analyses of the granules usually show positive staining for antibodies to S-100, vimentin, actin or neuron-specific enolase consistent with neural cell origin of the tumor. EGCT's vary in size from sub centimeter to more than 10 cm, and the symptoms are dependent on the size. EGCTs have been shown to infiltrate locally producing cough and hemoptysis. If the tumor is big enough, it can cause bronchial obstruction and can lead to recurrent infections, dyspnea and chest pain. There has only been one reported case of malignant GCT [29]. On bronchoscopy GCTs usually appear as firm small isolated nodules or polyps with overlying normal mucosa. In obstructive cases, it can cause destruction of the pulmonary parenchyma distal to obstruction and could warrant a pneumonectomy. Most of them can usually be managed endoscopically.

Our Experience

A 35 y/o African American male presented to us with long standing asthma. His symptoms included loud wheezes, louder on the right. A CT scan demonstrated a right hilar mass obstructing the right main bronchus (Figure 6). A therapeutic bronchoscopy was performed; this confirmed as exophytic mass obstructing the right main bronchus (Figure 7a). After Rigid bronchoscope intubation, microdebrider and argon plasma coagulation were used for debulking (Figure 7b). The pathology demonstrated numerous syncytial clusters and single cells with coarse granular cytoplasm. Figure 8a and b show a syncytium of cells with granular cytoplasm and bland nuclei. No cytologic atypia, mitoses or necrosis were present (Diff quick, 400x and Hematoxylin and Eosin stain, 600x), this supports a diagnosis of granular cell cancer. The patient is doing well and has had no recurrence of tumor at 24 months after the ablation.

Endobronchial Neurogenic Tumors/Schwannoma

Neurogenic tumors usually arise in posterior mediastinum but can very rarely be seen in the bronchus primarily. Fewer than 50 cases have been described in the literature [30]. Most of the cases are either neurofibroma or schwannoma. Neurofibromas are neural in origin and usually associated with neurofibromatosis I, while schwannomas can arise sporadically [31]. Neuro-fibromas are complex tumors composed of axonal processes, Schwann cells, fibroblasts, perineurial cells, and mast cells [32]. Neurogenic tumors are characterized by interwoven sheets of fusiform or spindle cells with indistinct cytoplasm and palisading nuclei [33]. Immunohistochemistry demonstrates positivity for S-100 protein. Clinical features of neurogenic tumors are similar to

other benign endobronchial tumors. It can cause obstructive symptoms when it enlarges. It can cause cough, chest pain, and dyspnea. Massive hemoptysis has been reported in the literature [34]. On bronchoscopy, benign neurogenic tumors appear firm, solid, encapsulated masses well demarcated from surrounding normal tissue. They can sometimes be cystic [33]. Complications can include massive hemoptysis leading to asphyxiation and death.

Endobronchial Mucous Gland Adenoma

Mucous gland adenomas are rare primary lung tumors. They comprise of less than 0.5% of all lung tumors. They are not associated with smoking and have a better prognosis than surface epithelial tumors [35]. Mucous gland adenomas arise from mucosal sero-mucous glands and ducts of trachea or bronchi [36]. The usual histologic findings include; acini lined by mucous secreting cells with a prominent cystic mucinous component. They are contained within the bronchus [37]. On immunohistochemistry, mucous gland adenomas are positive for high molecular weight keratins and negative for thyroid transcription factor-1 (TTF-1) [38]. Most of the patients with mucous gland adenomas are asymptomatic. Just like other endobronchial tumors, enlargement leads to obstructive symptoms. They can cause wheezing, atelectasis, infections, dyspnea and sometimes hemoptysis [35]. On bronchoscopy the tumor appears solitary, smooth and well circumscribed.

Endobronchial Pleomorphic Adenoma

Endobronchial Pleomorphic Adenoma (EPA) is also a rare primary endobronchial tumor. It accounts for 1% of all lung carcinomas [39]. It mostly occurs in the ages of 35 to 74. EPA appears to originate from a mixture of luminal-type ductal epithelial and myoepithelial cells [40]. Histology shows sheets or trabeculae of myoepithelial and epithelial cells in myxoid matrix. Necrosis and high mitotic activity correlates with potential to turn malignant. Immunohistochemistry should reveal both epithelial and myoepithelial components with positivity to cytokeratine (CK) 5, CK7, CK14, CK 17, CK 18, vimentin and smooth muscle actin [41]. Like other endobronchial tumors, the symptoms depend on size. They can range from being asymptomatic to extensive post obstructive parenchymal destruction. Patients can present with dyspnea, cough, fevers or hemoptysis. There have been reports of EPA turning malignant [42]. On bronchoscopy these tumors appear to be usually solid, white, well demarcated and uncapsulated. Cut surface is myxoid, whitish, soft and rubbery [43].

Squamous Papillomas

Solitary squamous papillomas

Solitary squamous papillomas (SSP) are the most common solitary papillomas. Estimated incidence of SSP is 3.95 cases/100,000 patients/year. The mean age of diagnosis is 54. They are more common in men that smoke [44]. HPV infection has also been associated with squamous papillomas. They arise of squamous epithelial cells lining the respiratory tract. Histologically, they are characterized by keratinizing or nonkeratinizing mature squamous epithelium lining papillary connective tissue stalks [45]. On Bronchoscopy, they usually appear as exophytic, tan, friable masses with occasional ulceration. Patients with SSP can be asymptomatic at presentation or present with obstructive symptoms like cough, dyspnea, and hemoptysis.

Recurrent respiratory squamous papillomas

Recurrent Respiratory squamous papillomas (RRSP) are caused by HPV infection of stem cells in basal layers of respiratory mucosa. They have bimodal age distribution, occurring in children (Juvenile

Onset RRRP) or occurring in adults around fourth decade of life (Adult Onset RRRP). Incidence of RRSP is around 4.3/100,000 children and 1.8/100,000 adults. They have the same histologic features like SSP. RRRP most commonly affects larynx and can cause hoarseness, upper airway obstruction, choking sensation and sensation of something stuck in the throat. Although benign, RRP is difficult to control, has a high recurrence rate causes severe morbidity and have a higher risk for malignant transformation [46].

Glandular Papillomas

Glandular Papillomas are very rare group of papillomas with only 21 cases reported in English Literature since 1954 [47]. They arise from the mucosal surface of the central trachea-bronchial tree. On histology, they appear as papillary stromal cores lined by pseudostratified or single layer of ciliated or nonciliated columnar cells admixed with cuboidal cells or mucin-filled cells. Cellular atypia or necrosis is not seen [45]. They can appear as friable, red to tan in color tumors ranging in size from 0.7 to 2.5 cm. Due to their endobronchial location, they can also cause obstructive symptoms like cough, dyspnea, recurrent infections or hemoptysis.

Mixed Squamous and Glandular Cell Papillomas

Mixed Papillomas occur predominantly in middle aged and older males. It has been associated with smoking. On histology, they show components of both squamous and glandular cell papillomas. Transitional urothelium-like morphology can be present between the two kinds of epithelium [48]. Immunological staining reveals positivity in all cells for CAM5.2, mucin MUC5AC, CK7, CK 19, CK5/6, TTF-1, indicating a common origin for different components of the tumor [1]. On bronchoscopy, they are hard to differentiate from squamous or glandular papilloma. Like other papillomas, they can cause obstructive symptoms. Recurrence has not been reported for mixed papillomas.

Bronchial Fibroepithelial Polyp

Bronchial Fibroepithelial Polyp (BEP) is an uncommon and poorly recognized endobronchial lesion, which has only been reported in literature as isolated case reports. The pathogenesis of these benign neoplasms has been attributed to chronic inflammatory etiologic factors. This includes chronic smoke inhalation, repeated airway infections, foreign body aspiration, prolonged mechanical ventilation and chronic inflammation in asthma and chronic obstructive pulmonary disease (COPD). Histologically, BEP consist of a fibrovascular core covered by normal respiratory epithelium [1]. BEP's are usually asymptomatic. When symptomatic, patients present with recurrent respiratory infections like pneumonias, refractory asthma, dyspnea or hemoptysis [49] While radiologic studies are usually ineffective in identifying the polyp, it highlight a possible inciting etiology, such as a foreign body or a broncholith. Lesions larger than 10 mm may also be visualized on CT scan. On bronchoscopy, the lesions appear as a firm nodule with a hard consistency and a whitish, glistening, smooth surface. While most patients exhibit good clinical course after resection, relapse has been reported in an isolated case report [50].

Treatment and Outcomes

We suggest following management approaches for a patient diagnosed with a benign endobronchial tumor.

Observation: This approach is reserved for asymptomatic patients and in whom the lesion more than likely to be benign based on the clinical context and radiographic findings. A trial of steroids or antibiotics can be given if the lesions are thought to be secondary to

a chronic inflammatory process. Trial of cytotoxic agents and antiviral agents may be done in case HPV is the suspected etiology of the lesion. This approach is especially suited to patients with multiple lesions, in whom debulking may not be practical.

Endoscopic intervention: With recent advancements in bronchoscopic techniques and instruments, this has become the first line of offence in management of endobronchial tumors. In patients with good overall status and minimal comorbidities flexible Bronchoscopy under local anesthesia is usually adequate. Rigid bronchoscopy under general anesthesia is preferred if procedure is anticipated to be prolonged (30 minutes or more) or poor cardio-pulmonary reserve is evident. Multiple debulking techniques including Nd: YAG laser, Argon plasma coagulation, electro cautery snare, ethanol injection and microwave solidification are available for use with or without a rigid bronchoscope [51]. The advantages and disadvantages of these techniques are summed in Table 2.

Our approach to endobronchial lesions includes, a diagnostic flexible bronchoscopy with or without endobronchial ultrasound for diagnosis and planning. If the lesion is small and pedunculated, we usually use an array of techniques (snare, forceps or needle knife) to excise the lesion during the first setting itself. For broad based, large or vascular, and loss of airway from tumor or bleeding is possible, the debulking procedures are performed through a rigid bronchoscope at a later date.

Surgical interventions: Indications for surgical intervention are, (a) histologic specimen cannot exclude malignancy from the differential, (b) significant bronchiectasis and/or organizing pneumonia post obstruction by the tumor, (c) tumor infiltration into bronchial wall or (d) there is airway distal to tumor obstruction (drowned and atelectatic lung) [52]. In pursuing this particular approach the use of tissue sparing

Methods	Pros	Cons
ND: YAG Laser	1) Higher heat can be delivered. 2) Treatment of choice for emergency airway maintenance.	1) Risk of airway fire when used with high concentration of oxygen precluding its use 2) Caulterization of large tumors can cause temporary airway edema and stenosis 3) Increased risk of hemorrhage and airway perforation.
Microwave solidification	1) Weak cauterization power. 2) Can be used with high oxygen due to minimal smoke production 3) Can be used for tumors located at acute angles	1) Weak cauterization power precludes use in large tumors
Argon Plasma Coagulation	1) Decreased bleeding 2) Decreased risk of wall perforation 3) Bends around corners	1) Slow method
Electro-cautery snare	1) Strong heating action can be used for tumor solidification and tumorectomy 2) Treatment of choice for obstructive tumors in poorly vascularized areas 3) Unlike other modes, No histological change induced in tumor specimen	1) Can cause deep heat denaturation in the bronchial wall 2) Cannot be used for wide based tumors
Microdebrider	1) Rapid debulking without heat injury 2) May not reach distal airways	1) Cannot be used on vascular tumors 2) Can cause airway injury rapidly

Table 2: Interventional techniques for benign endobronchial tumors [54-56].

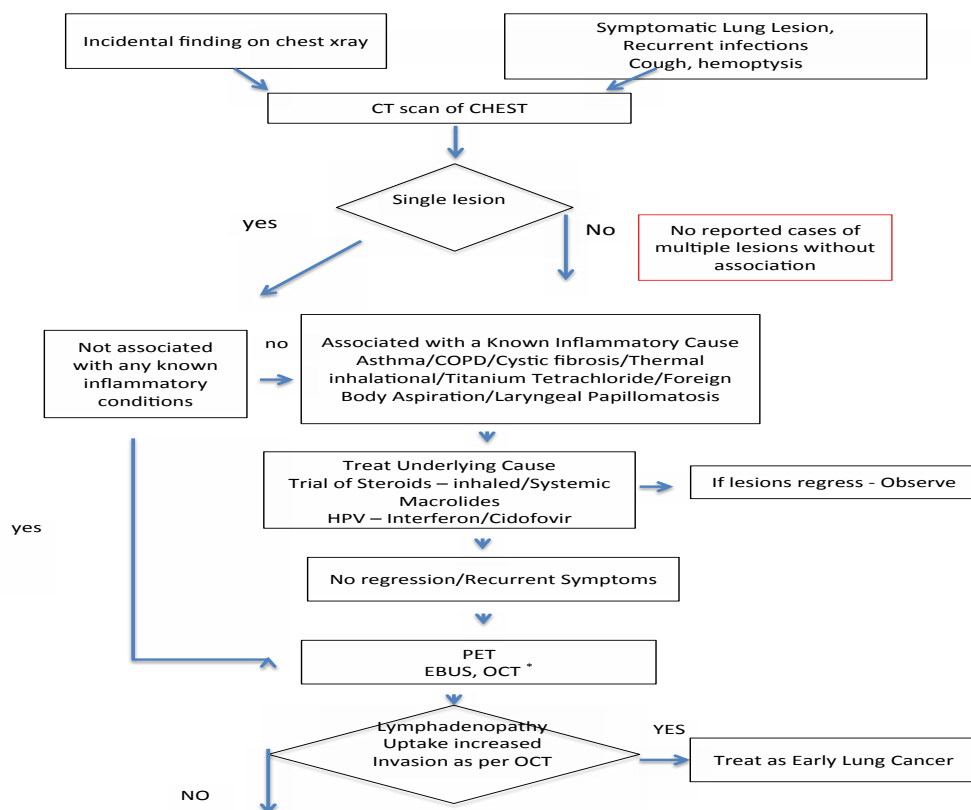


Figure 9: Outlines an algorithmic approach to patients with endobronchial lesions.

techniques must be accomplished with minimal parenchymal resection [53].

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