Bronchoscopic diagnosis and treatment of endobronchial carcinoid: case report and review of the literature

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Endoscopic resection of bronchial carcinoids may be a feasible and safe treatment option for patients with localised tumour manifestation, who are not suitable for or who are unwilling to undergo thoracic surgery https://bit.ly/33yKgwm

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ABSTRACT Carcinoid tumours are rare neuroendocrine neoplasms that mostly occur in younger adults with low tendencies to metastasise. Based on their histological characteristics, they are divided into typical and atypical subtypes. The most common presenting symptoms are due to central airway obstruction.

The first step in the diagnostic assessment should be a computed tomography (CT) scan, as it provides information both for local tumour extent and lymph node involvement. Bronchoscopy is the main tool for histological confirmation, evaluation of bronchial wall invasion and removal of endobronchial manifestation with subsequent resolution of atelectasis. Endobronchial ultrasound may be necessary to rule out lymph node metastasis. Somatostatin receptor scintigraphy in combination with CT can rule out further metastatic disease.

Surgical resection using parenchyma-sparing techniques remains the gold standard for treatment. For selected patients, endobronchial therapy could be an alternative for minimal invasiveness. Long-term follow-up is suggested due to the high likelihood of recurrence.

Here, we describe our clinical experience in a 35-year-old male patient who originally presented with haemoptysis and a central polypoid tumour in the left main bronchus revealed by a CT scan. The histological characteristics were indicative of a typical carcinoid. The patient was treated using an endobronchial approach only. No complications and no recurrences have been observed in a follow-up of 2 years.

Introduction

Bronchial carcinoid tumours were historically defined as bronchial adenomas and were considered benign, with good clinical prognosis [1]. In 1944, Engelbreth-Holm [2] postulated that some of these neoplasms

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were more aggressive and tried to establish a distinction between two different entities, typical and atypical carcinoid tumours. Later, in 1972, Arrigoni *et al.* [3] suggested differentiation criteria for these two types of carcinoid tumours based on the dissimilar histological features observed. The evidence from studies in the past decade revealed that these carcinoid tumours are distinguishable not only by their histology but also by their clinical and radiological presentation and, above all, their prognosis and treatment.

Epidemiology and prognosis

Carcinoid tumours account for approximately 2–5% of all lung tumours. Typical carcinoid tumours represent 90% of carcinoid lung neoplasms and 1–2% of lung tumours in general [4]. Moreover, lymph node metastasis has been observed in 5–15% of these patients at presentation, while in up to 3% of patients distant metastases are revealed during staging evaluation. Atypical carcinoid tumours are rare lung tumours (0.1–0.2%), presenting with lymph node metastases in 40–50% of patients and distant metastases in 20% [5]. Typical carcinoids occur mostly in younger patients, in contrast to atypical carcinoids, and a Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung found that the incidence of these tumours also differs between the sexes. Atypical carcinoid tumours occur less often among women [6]. Additionally, there are rare familial cases of pulmonary carcinoids [7]. Up to 5% of patients with multiple endocrine neoplasia type 1 develop pulmonary carcinoids, usually typical carcinoids and less often atypical carcinoids [8].

Typical carcinoids are less aggressive with 5-year survival rates of 87–100% and 10-year survival rates of 82–87%. Atypical carcinoids have a more malignant behaviour with significantly lower 5- and 10-year survival rates of 50–95% and 38–75%, respectively [9, 10]. A recent review showed that tumour size, histology of atypical carcinoids, and lymph node metastasis have negative impacts on survival from pulmonary carcinoids [10]. Regarding tumour diameter, Yang *et al.* [11] showed that in patients with carcinoid tumour sizes $\geqslant$3 cm, prognosis was significantly worse than for those with tumour sizes <3 cm. Poor outcome in patients with atypical carcinoid histology is correlated with larger tumour size and location in the lung periphery, as well as with increased incidence of metastatic lymph node affection [12, 13]. Surgical treatment is not excluded as a therapeutic option in patients with metastatic lymph node disease. Complete resection can have a positive effect on survival for patients with both typical and atypical carcinoids [14]. 5-year survival rates for lymph node involvement in patients with typical carcinoids are 92–100%, though 10-year survival rates drop to 50%. Comparably, 5- and 10-year survival rates for lymph node positivity in patients with atypical carcinoids are 25–78% and 25–59%, respectively [15, 16].

Histology

Bronchial carcinoids are classified as neuroendocrine neoplasms. They arise in the bronchial and bronchiolar epithelium and their origin cell type is either Kulchitsky cells, neuroepithelial bodies or pluripotent bronchial epithelial stem cells. Histologically, bronchial carcinoids tend to organise in cellular nests or bands and are easily recognised using routine microscopic techniques due to their rich fibrovascular stroma, which is a specific feature of their neuroendocrine origin [5]. They can be distinguished from other tumours by the variable expression of genetic markers linked to the p53 locus of chromosome 17p13 [17]. Chromogranin, synaptophysin and neural cell adhesion molecule/CD56 are common neuroendocrine cell markers for carcinoids, while thyroid transcription factor 1 is negative for centrally located carcinoids and positive for those in the lung periphery [18, 19]. Furthermore, they synthesise, store and secrete a variety of peptide hormones and neuroamines such as serotonin, somatostatin, bradykinin and adrenocorticotropic hormone [19]. The wide spectrum of bronchial carcinoids includes tumourlets and typical carcinoids as benign neoplasms and atypical carcinoids, large cell neuroendocrine carcinomas and small cell lung cancers which have higher malignant potential [20]. In order to separate typical from atypical carcinoids, the 1999 World Health Organization classification accepted the criteria proposed by Travis [21] based on the correlation between histologic differences and clinical prognosis of the patients. Histologic diagnosis of atypical carcinoids consists of a reduction in the lower limit of the number of mitoses observed from 5 to 2 per 10 high-power fields (HPF) and/or the presence of necrosis [21].

Symptoms and radiological features

As many as 40% of patients may present with cough (35%), fever, wheezing, chest pain and/or recurrent infections due to central airway obstruction [4, 22, 23]. Due to high vascularisation of bronchial carcinoids, 23% of patients also experience haemoptysis [23]. Carcinoid syndrome can be detected in 1% of patients as a result of systemic release of vasoactive agents, especially serotonin [4]. However, in about 30% of patients, diagnosis of carcinoids may be incidental, given the fact that patients can be symptom-free for a long time [24].

Although it is sometimes difficult to differentiate between typical and atypical bronchial carcinoids on radiologic images, some features seem to be representative of typical carcinoids. About 75–77% of typical carcinoids have a central location in the main, lobar or segmental bronchi [24, 25]; 16–40% of tumours have a peripheral position, showing as round or oval homogeneous opacities. Usually, typical carcinoids are found in the right lung (60% of patients) and particularly in the middle lobe [23]. In about 30% of patients, there is evidence of isolated or diffuse calcifications. Hilar, perihilar or endobronchial masses, and features of bronchial obstruction, can be characteristic of carcinoid radiologic imaging [26].

Functional somatostatin receptor (SSTR) imaging with the use of conventional somatostatin receptor scintigraphy contributes to the diagnostic evaluation of metastatic disease. The usefulness of 2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) for typical carcinoids may be limited by the potentially low uptake of ^{18}F-FDG [27]. Conversely, atypical carcinoids usually present with increased ^{18}F-FDG uptake with variable uptake of radiolabelled somatostatin analogues [28]. A somatostatin analogue, ^{68}Gallium (^{68}Ga) DOTATOC, used as a tracer in PET-CT scanning, introduced a new era of evaluation and staging for pulmonary neuroendocrine tumours, with a diagnostic accuracy >95% for typical carcinoids [28, 29]. Overall, ^{68}Ga DOTATOC has a high negative predictive value in diagnosing typical carcinoids, but not atypical carcinoids [30]. In a recent meta-analysis, JIANG *et al.* [31] suggested a possible combination of these two tracers (^{18}F-FDG and ^{68}Ga) with the use of the ratios of maximum standard unit value on (^{68}Ga) DOTATOC and FDG-PET/CT for prediction of the histological type of pulmonary carcinoids.

Bronchoscopic findings and tools for assessment

Bronchoscopy is the mainstay of diagnostic evaluation for pulmonary carcinoids. In 75% of cases, bronchoscopy highlights budding well-vascularised, well-rounded lesions that are raspberry coloured and which have a risk of bleeding during biopsy sampling. Most carcinoid tumours are accessible with endobronchial biopsy, since 75–77% are centrally localised [24, 25]. Transbronchial or percutaneous needle biopsy can be used for peripheral tumours [24].

While a preoperative CT scan can be safely used as a first approach for lymph node involvement in patients with bronchial carcinoids, with a specificity of 90–93% [32], bronchoscopy with endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration demonstrated superiority over CT scanning in mediastinal lymph node evaluation [33]. Thus, for tumours >3 cm [34, 35] or those with histopathology of atypical carcinoids [25, 36], which tend to be metastatic to lymph nodes, EBUS with a convex probe should be added to the algorithm for pre-treatment evaluation. In addition to ruling out lymph node metastasis with convex probe EBUS, EBUS with a radial probe allows the evaluation of bronchial wall invasion [35]. More specifically, in a small study (18 patients) by BOSTANCI *et al.* [37], EBUS using a 20 MHz-radial probe with balloon revealed superficial infiltration of the bronchial wall with the tumour in three patients, while high-resolution CT only identified atelectasis and no lesions. Whether or not EBUS with a radial probe increases the diagnostic yield for peripheral pulmonary carcinoid tumours remains to be confirmed in methodologically sound, randomised controlled studies [38–40].

Treatment

Surgical resection, using either anatomical resection (lobectomy, bilobectomy and pneumonectomy) or a parenchyma-sparing technique (segmentectomy, sleeve lobectomy, bronchial sleeve, wedge or enucleation of the tumour), remains the gold standard treatment for carcinoids. Studies looking at anatomical resections show higher recurrence rates of malignancy compared with parenchyma-sparing resection studies [10]. BOLUKBAS and SCHIRREN [41] suggested that, for typical carcinoids, parenchyma-sparing resections should be favoured over anatomical resections. For patients with atypical carcinoids and a higher possibility of lymph node involvement, radical surgery is recommended. FILOSSO *et al.* [42] performed a retrospective study for surgical management of bronchial carcinoids and found that relapses developed in 19.5% of atypical carcinoid tumours after radical excision and lymph node sampling. The EMETNE-SEPAR study found an overall 5-year survival of 78% for patients with atypical carcinoid tumours (60% for patients with positive lymph nodes) and suggested lymph node dissection during surgery [6]. Furthermore, a database analysis from 441 patients in the USA with atypical carcinoids reported a 3-year survival rate of 67% for surgical resection [43]. Although atypical carcinoids have a higher tendency for metastases than typical carcinoids, patients with small intraluminal tumours and no signs of lymph node involvement might be ideally suited for lung parenchyma-sparing procedures [12, 44].

Endoscopic approaches may be added to the therapeutic armamentarium for bronchial carcinoids in selected cases [13, 45, 46]. Laser therapy, cryotherapy or argon plasma coagulation have been used for methods of endobronchial treatment (EBT). In most of the published case series to date, a multi-modality approach has been used, combining several of the above mentioned techniques to achieve complete

resection and removal of microscopic tumour residuals at the tumour base (table 1). Because of the low-grade nature of carcinoids, patients with intraluminal tumours ⩽2 cm, volume <5 cm^3 and a small base attachment (<1.5 cm^2), without lymph node involvement or suspected locoregional or distant metastasis, may be eligible for EBT [35, 51]. Tumours with a diameter ⩾3 cm often present with advanced histology and have worse outcomes; as a result patients with lesions >2 cm should ideally be referred for surgical treatment [25]. Furthermore, extraluminal disease on CT scan is associated with a lower success rate for EBT [10]. Based on the study of Reuling *et al.* [35], only 28% of patients with carcinoid lesions <20 mm, with probable extraluminal growth on CT scan, were successfully treated with EBT. In contrast, Petrella *et al.* [52] argued that only 5–10% of all bronchial carcinoids are polyp-like lesions without extensions through the cartilaginous wall. The authors suggest that bronchoscopy and CT scan should be performed within 6 weeks of EBT to assess the success of the approach. In lesions with large bases, local persistence, however, cannot be ruled out [52]. The need for lymph node resection is a bone of contention, since some studies reported no difference in survival between patients with typical and atypical carcinoids treated with parenchyma-sparing resections (including EBT) without lymph node dissection [13, 53], while other studies showed an important prognostic probability for nodal status in atypical carcinoid [54, 55]. As a result, the preoperative classification of carcinoids as typical or atypical along with evaluation of lymph node involvement is necessary in order to decide how to manage patients with EBT [35].

In contrast, Reuling *et al.* [35] showed a high success rate of up to 72% for patients with pure endoluminal tumours <20 mm diameter who were treated with EBT. In this study, successful treatment was defined as the absence of residual disease during the first 2 years of follow-up with CT and bronchoscopy after EBT [35]. In the majority of studies the locoregional and distant recurrence rates were lower in EBT-treated patients (0–5% and 0–4%, respectively) (table 1) [47, 48, 50], than in surgically treated patients (0–8% and 8–23%, respectively) [10, 13]. These findings, however, should be interpreted with caution due to an inevitable selection bias, as patients with more extensive disease were selected for surgery.

Even in the event that EBT cannot achieve radical management, this technique may offer a number of benefits for patients, including the removal of bronchial obstruction with potential resolution of post-obstructive pneumonia and the optimisation of the subsequent surgical resection by the precise definition of tumour borders [44].

Follow-up

Typical versus atypical carcinoids

There is no consensus on the timing and modality of follow-up after surgery or parenchyma-sparing procedures. In the EMENT-SEPAR study with a median follow-up of 10 years after surgery, local recurrences differed significantly between patients with typical (0.88%) and atypical carcinoids (3.26%) [6]. Lou *et al.* [56] reported a 5% recurrence rate for typical carcinoids and 26% for atypical carcinoids after a median follow-up of 3.5 years in 337 patients with surgically resected neuroendocrine tumours of the lung. Moreover, 76% of recurrences occurred in the first 5 years with annual rates between 10–19% [56]. Another recent study, after a 10 year follow-up in surgically treated patients with pulmonary carcinoids,

TABLE 1 Studies evaluating different techniques for endobronchial therapy in carcinoids the past 10 years

	First author [ref.]	Patients n	Histology AC/TC	Median follow-up months	Recurrence rate # %
Biopsy forceps	Luckraz [16]	28	0/28	105¶	6
Laser					
YAG laser or laser therapy	Cavaliere [47]	38	0/38	Up to 198	0
	Fuks [48]	10	0/10	29	0
	Neyman [49]	16	0/16	36	6
Multi-modality					
YAG laser/cryotherapy	Bertoletti [45]	18	0/18	55	9
	Brokx [13]	47	5/42	114	12
YAG laser/ electrocautery/mechanical excision/ cryotherapy	Reuling [35]	125	19/106	82	8
YAG laser/APC/electrocautery/cryotherapy	Boyaci [50]	14	0/10	32±19.22	0
Diode laser/APC/cryotherapy	Dalar [46]	29	5/24	49	0

AC: atypical carcinoid; TC: typical carcinoid; APC: argon plasma-coagulation. #: recurrence rate refers to both loco-regional and/or distant relapses; ¶: mean value.

showed local recurrences in 7.8% of patients and distant metastases in 8.9% of patients, with the majority (80%) of patients being diagnosed with atypical carcinoid [57]. In this study, the time from surgery to local recurrence ranged from 2 months to 3 years, while the time from surgery to distant metastasis ranging from 5 months to 4 years [57]. For EBT, patients are selected for the presence of well-defined carcinoid tumours with histology of typical carcinoids. As a consequence, lower recurrence rates are observed during follow-up [8].

Carcinoids with or without lymph node involvement

A study by the European Society of Thoracic Surgeons Lung Neuroendocrine Tumors Working-Group Steering Committee revealed 9% and 36% lymph node involvement at diagnosis in patients with typical and atypical carcinoids, respectively [58]. This result is in accordance with the EMENT-SEPAR study, in which nodal involvement was a factor with a high prognostic value [6]. Cardillo *et al.* [14] reported on 163 patients treated with radical mediastinal lymphadenectomy for bronchial carcinoids, with a follow-up period of 12 years. The authors confirmed that the difference in 5-year survival rates between carcinoid subtypes was predominantly associated with the nodal status, rather than the histologic subtype, with N2 (nodal status) being the most important prognostic factor.

Although most recurrences occurred in the first 5 years after surgical resection in patients with atypical carcinoid [56, 57], patients with typical carcinoids have better prognoses, even in the presence of a relapse [10, 59]. So, current guidelines suggest a long-term follow-up in view of the risk of late relapse reported in the scientific literature [59, 60]. Annual CT scans of the chest might be a necessary part of the evaluation for at least 10 years after resection. More specifically Brokx *et al.* [13] suggested repeated high-resolution CT and fibreoptic bronchoscopy every 6 months for the first 2 years, then annually up to 5 years and a yearly check-up by the pulmonologist.

Case report

Our patient is a 35-year-old male never-smoker with two episodes of haemoptysis (<5 mL) for 2 days that resulted in referral to a physician 3 years ago. There was no fever, chest pain, loss of weight or weakness. There was no history of any other chronic disease. A CT scan with intravenous contrast revealed a 7-mm round, solid lesion with contrast uptake in the left main bronchus (figure 1a). There was no consolidation or volume reduction of the left lung or enlargement of lymph nodes. Functional respiratory tests have been carried out to screen for airway obstruction and to assess for any perioperative risk with no specific findings.

The patient underwent combined rigid bronchoscopy with flexible bronchoscopy. A rounded, well-vascularised polypoid lesion of 9 mm in diameter was detected in the left main bronchus, approximately 2 cm distal from the main carina, located at the medial airway wall (figure 1b). An electrocautery snare was used in order to remove the lesion in toto using cutting and coagulating phases with an automatic control of peak voltage (Erbe VIO 300 D, EndoCut Mode).

Histopathology revealed a neuroendocrine tumour without signs of necrosis and with one mitosis observed per 10 HPF. Immunostains were positive for synaptophysin and chromogranin, while the Ki67

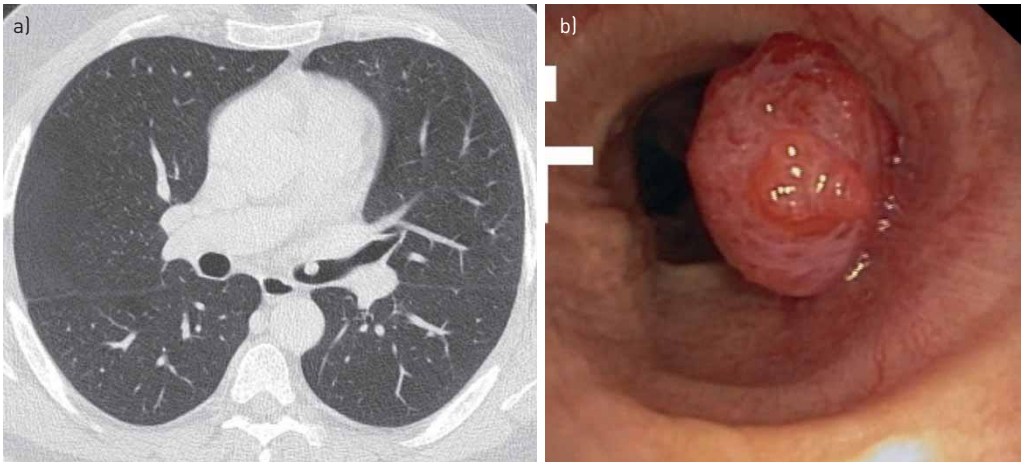

FIGURE 1 a) Initial computed tomography scan with an endobronchial lesion in the left main bronchus. b) Initial bronchoscopy with an exophytic well-vascularised polypoid lesion.

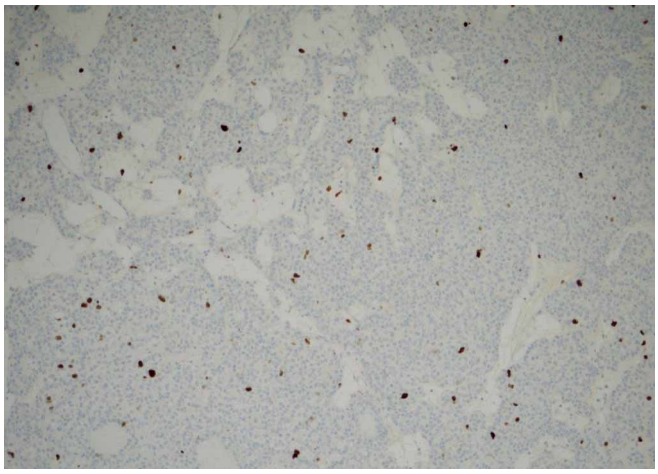

FIGURE 2 Histopathology image with immunostaining for synaptophysin and chromogranin; <1% of tumour cells showed positivity.

proliferation index was <5% (figure 2). All the above histologic findings were consistent with a typical carcinoid tumour.

Although there were no symptoms of paraneoplastic syndrome, the patient underwent laboratory testing for adrenocorticotropic hormone, serotonin and urinary 5-hydroxyindoleacetic acid levels, which were normal. Further imaging including abdominal CT as well as (^{68}Ga) DOTATOC PET scintigraphy did not reveal pulmonary or extrapulmonary pathology.

After discussing all available therapeutic options (EBT or sleeve resection), the patient opted for an EBT.

A second bronchoscopy was performed 6 weeks later. Upon inspection there were no specific alterations other than scarring type of tissue. Using a 1.9-mm cryobrope (Erbebkryo 2 Workstation, Erbe, Germany) guided through the working channel of the bronchoscope, multiple biopsies were obtained at the base of the previously resected lesion. The probe tip was cooled for ∼2–5 s maximum, using visual feedback of the ice font at the tip of the probe. The decision to use a cryoprobe was based with the intent of combining biopsy with potential local cryotherapy of any potential microscopic tumour remnants [61]. Subtle local bleeding was controlled easily using argon plasma point coagulation to achieve focused haemostasis. Histology did not reveal any signs of carcinoid at these follow-up biopsies.

Endoscopic follow-up thereafter was performed at 6 months, 1- and 2-years including CT scans and flexible bronchoscopy with re-biopsies at the former tumour base area. There was no evidence of local recurrence (figure 3). The patient has so far remained asymptomatic.

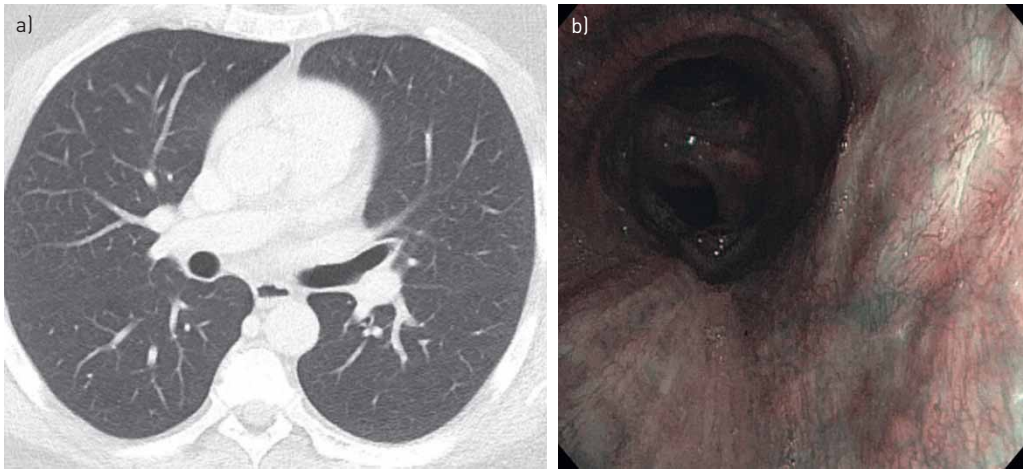

FIGURE 3 Follow-up at 2 years: a) computed tomography scan and b) bronchoscopy with narrow band imaging (NBI) to check for local recurrence. NBI uses a unique filter to select light wavelengths that are preferentially absorbed by haemoglobin, thereby permitting superior microvasculature detection compared with conventional bronchoscopy [62]. As angiogenesis occurs preferentially in dysplastic or neoplastic lesions, NBI aids in early assessment of local recurrence.

Discussion

Bronchoscopy is usually used to obtain tissue sampling for the diagnosis of a pulmonary carcinoid. Whether a flexible bronchoscopy, or flexible bronchoscopy in combination with rigid bronchoscopy, should be performed is up to institutional practice and physician experience. Rigid bronchoscopy under general anaesthesia may further offer improved local bleeding control if necessary. However, a study by Gao *et al.* [63] showed that severe bleeding in patients with bronchoscopic biopsies of endobronchial carcinoid is rare and may not be necessarily related to the vascular tumour appearance of the lesion or the history of recent haemoptysis, consistent with the observations in the present case report.

Even though carcinoids of the lung have better prognosis than carcinoma, the gold standard for treatment in most cases should be surgical resection [59]. Surgeons may have to weigh up radical resection with lung parenchyma-sparing techniques, as the rate of local recurrences after surgery remains low overall. While lobectomy or segmentectomy are the methods of choice for peripheral tumours, sleeve resection or sleeve lobectomy are the best option for centrally located lesions [42].

However, the majority of carcinoids, especially typical carcinoids, grow centrally in one of the main bronchi, which generally makes them accessible for a bronchoscopic approach [16, 44]. Endoscopic resection might thus serve not only for histopathologic diagnosis, but also in resolution of pneumonia from bronchus obstruction, evaluation of tumour borders (in addition to CT), as first-line therapy before surgery or, in selected cases, as the only therapy for patients who are medically unfit or unwilling to undergo surgery (figure 4) [13, 16, 64].

According to previous studies, the overall complication rate for surgery ranges from 1% to 63% with lower rates for EBT, ranging from 0% to 30% [10]. Prolonged air leak, respiratory tract infections, cardiac

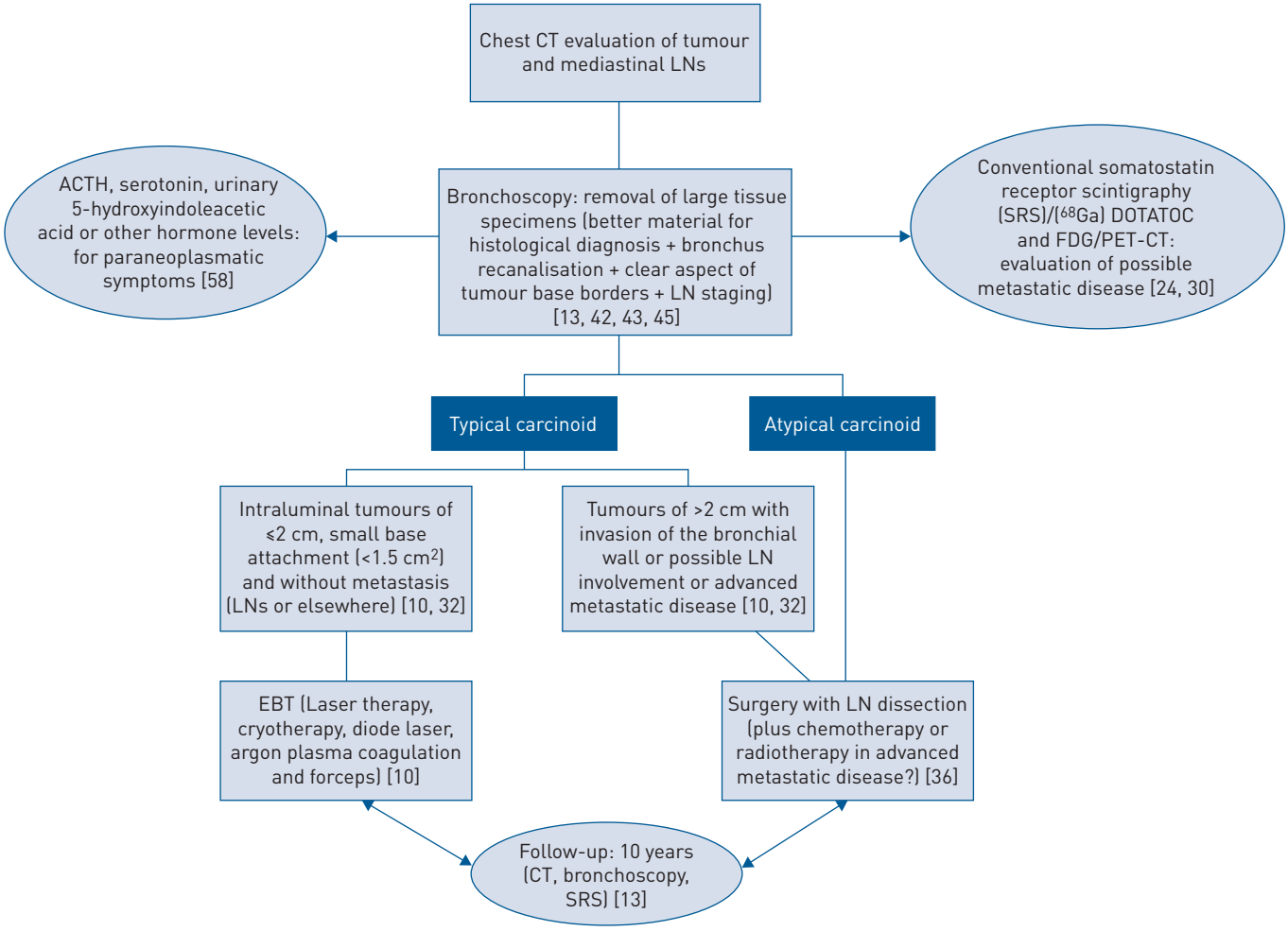

FIGURE 4 Algorithm for the assessment of bronchial carcinoid. CT: computed tomography; LN: lymph node; ACTH: adrenocorticotropic hormone; SRS: somatostatin receptor scintigraphy; FDG: 2-fluoro-2-deoxy-D-glucose; PET: positron emission tomography; EBT: endobronchial therapy.

arrhythmias, empyema and bronchial stenosis were frequently reported as complications after surgery. In contrast, few complications arise from endobronchial interventions [10, 49]. The occurrence of restenosis of affected airways, occurring within 2 months to 4 years after the procedure, has been reported with a range between 24% and 28% [61, 65]. Our patient had no signs of local or distant recurrence noticeable during follow-up bronchoscopies within a period of 2 years. Consistent with previous studies [45, 46, 66], beyond using an electrosurgical removal technique, local cryotherapy (as part of the follow-up local sampling procedure) has been used in order to treat any potential microscopic tumour residuals. In the absence of randomised controlled trials comparing individual or combined EBT techniques, the best approach for endoscopic therapy of localised carcinoids has yet to be determined.

In conclusion, EBT provides an alternative treatment for typical carcinoids. Its minimally invasive nature in combination with locoregional advantages (bronchus recanalisation and better evaluation of tumour borders) make it an appealing therapeutic approach for patients with intraluminal located carcinoids. We believe that the management of carcinoids requires prospective trials together with high-quality patient registries, in order to identify the most appropriate treatment modality in affected patients.

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