Bronchial Carcinoid Tumours in Children – A Review

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Abstract

Bronchial carcinoids (BCs) are rare, well-differentiated malignant neuroendocrine tumours that account for 2–5 % of all lung neoplasms in adults. In paediatric patients, carcinoids represent the most frequent primary lung cancer. Although BCs in childhood often have an endobronchial location causing airway obstruction, they are frequently misdiagnosed as benign conditions, resulting in a delay in definitive diagnosis and treatment. Surgery represents the treatment of choice for BCs, and lung-sparing resections (sleeve or bronchoplastic procedures) are recommended in central carcinoid tumours; pneumonectomy should be avoided, particularly in childhood. If promptly diagnosed and radically treated, BCs in children have an excellent prognosis. Relapses can occur many years after a radical resection, highlighting the necessity for long-term follow-up.

Keywords

Bronchial carcinoid tumours, paediatric lung neoplasm, typical carcinoid, lung surgery, bronchoscopy, sleeve resection, bronchoplasty

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Carcinoid tumours are rare, malignant neuroendocrine neoplasms first described in 1888 in the ileum[1] and called 'Karzinoide' by Oberndorfer in 1907.[2] Neuroendocrine cells were originally called clear cells and later amine precursor uptake and decarboxylation (APUD) system cells.[3] The term neuroendocrine was introduced with the finding that these cells are capable of producing bioactive amines and that a number of these cells are identical to those of the nervous system. Neuroendocrine tumours of the lung arise from bronchial mucosal cells known as enterochromaffin cells or Kulchitsky cells, which are part of a diffuse neuroendocrine system. For many years the carcinoid tumour of the lung was called bronchial adenoma, which comprised other bronchial tumours with benign behaviour. Today, bronchial carcinoids (BCs) are classified as well-differentiated malignant neuroendocrine tumours in two distinctive forms – typical carcinoid (TC) and atypical carcinoid (AC) – with different histological features, clinical course and prognosis. The differences in histological criteria between TC and AC were first described by Arrigoni et al.[4] and later modified by Travis et al.[5] They were fixed in 1999 by the World Health Organization (WHO).[6]

Pathology

TC is a variant of neuroendocrine tumours with a low-grade histological malignancy profile (<2 mitoses/10 high-power field [HPF], nuclear pleomorphism and absence of necrosis) that rarely metastasises.[7,8] AC is considered to be an intermediate grade of malignancy; it presents with ≥2 but <10 mitoses/HPF and/or coaugulative necrosis.[5] Several immunohistochemical markers have been considered for the histological assessment and risk stratification of carcinoids. In terms of tumour cell commitment, carcinoids are consistently associated with the immunohistochemical expression of neuroendocrine markers (chromogranin A, neuron-specific enolase [NSE], synaptophysin, Leu7).[9] Mib1 and Bcl2 expression is an independent variable associated with tumour prognosis (with no statistical interaction between the two). In the future, such a biologically plausible immunohistochemical pattern could also be suitable in the routine histological assessment of BC.[10]

Recently, researchers have studied the importance of genetics in BC. A recent paper reports that in TC and AC DNA, under-representations of 11q are frequent and that in AC there are also frequently losses of 10q and 13q, as in high-grade neuroendocrine malignant tumours (large- and small-cell lung cancer). Losses of 10q and 13q probably suggest a more aggressive behaviour of AC.[11]

Epidemiology

BC is a rare entity in the paediatric population and the true incidence is difficult to establish because in old reports BCs were mentioned as bronchial adenomas. BCs make up 80–90 % of the group of tumours that were formerly classified as bronchial adenomas and included adenoid cystic carcinomas and mucoepidermoid carcinomas.[12] In many successive papers a correct histological review of the specimens was not undertaken. In children metastatic lung tumours greatly outnumber primary lung lesions.[13] Among primary lung tumours in childhood, malignancies are three times more frequent then benign neoplasms (papillomas, leiomyomas, haemangiomas, inflammatory myofibroblastic tumours and hamartomas).[14]

In literature from the past 20 years we have found only four papers that report five or more cases of BC tumours in paediatric patients;[12,15–17] it is thus difficult to establish the true incidence.

Table 1: Number and Characteristics of Bronchial Carcinoid Tumours in Children in the Literature

Authors	Number	Age (years) (range; median)	Sex (M/F)	Symptoms	Site (R/L)	Treatment Classic/ Parenchyma-saving	Histology (TC/AC)	n	Recurrence	Follow-up/Status
Wang, et al. 1993[12]*	17	10–21; 17	8/9	Atelectasis 59 % Pneumonia 53 % Wheezing 47 %	11/6	10/7	17/0	1	2	All alive (2 metastasis) Mean 6.5 years [0.5–34]
Al-Qahtani, et al. 2003[15]	5	10–15; 13	3/2	--	4/1	4/1	5/0	0	0	All alive Mean 30 months [6–48]
Fauroux, et al. 2005[17]	11	9–15; 13	5/6	Pneumonia 70 % Haemoptisis 35 %	7/4	10/1	11/0	1	0	All alive Mean 4.3 years [1–10]
Rizzardi, et al. 2009[16]	15	8–18; 15	11/4	Pneumonia 80 % Cough 6.6 % Haemoptisis 6.6 % Fever 6.6 %	9/6	5/10	13/2	3	2	1 dead (not for BC) 14 alive (1 metastasis) Mean 10 years [3–32]

**This paper includes patients up to 21 years of age.*

Nevertheless, BCs are the most common primary lung neoplasms of childhood,[14] accounting for up to 80 % of malignant pulmonary neoplasms in paediatric populations.[18,19] Their incidence is apparently increasing, although this is probably related to the introduction of more sensitive diagnostic tools as well as to an overall increased awareness of this disease among physicians.

Lung masses in children are approximately 10 times more likely to represent a benign developmental or reactive lesion than a neoplasm;[13] common malformations forming solid and cystic masses of paediatric lung include bronchogenic cysts, segmental bronchial atresia, sequestration and congenital bronchial malformation. The vast majority of solid parenchymal lung masses in children represent inflammatory, infectious or reactive processes with a differential diagnosis including granulomatous inflammation (fungal, mycobacterial, parasitic, sarcoidosis and vasculitis), abscess, pneumonia, septic embolus, infarction and haematoma.[20] A differential diagnosis should also be made with foreign bodies that are not uncommon in children.

To date, the aetiological factors predisposing infants and children to the development of pulmonary neoplasms are unknown. Diagnosis in the majority of cases occurs in adolescence with a mean age of 12–15 years,[16,17] but diagnosis delay is highly variable and is probably many months. The youngest case described in literature was at three years of age,[21] but the operation and the histological diagnosis were made three years later. In the few published series, the reported incidence is the same in both sexes[15,17] in the adult population[22] or shows a prevalence of carcinoids in males (male/female ratio 2.75).[16]

Clinical Presentation

Given the rarity of BC, clinical detection in children remains a challenge. In paediatric populations all BCs are centrally located in the bronchial tree. A tumour visualised in the bronchial tree by bronchoscopy or associated with atelectasis or obstructive pneumonia is commonly defined as 'central'.

In contrast to the adult population, younger patients are all symptomatic and the most common symptom is obstructive pneumonia with recurrent pulmonary infections in the same location.[12,16] Other symptoms include persistent cough, haemoptysis, wheezing and recurrent fever. These symptoms are aspecific, but their recurrence in a child with obstructive pneumonia localised in the same lobe, persistent cough or wheezing not responsive to the usual therapy should alert the physician and suggest diagnostic procedures such as chest X-ray and bronchoscopy. Although many authors[21,23] have stressed the importance of such symptoms (including asthma) for early diagnosis, many patients still undergo invasive diagnostic procedures too late, often after a symptomatic course of several months.

The characteristics of patients and clinical, surgical, pathological and follow-up data of the major recent reports in paediatric populations are summarised in *Table 1*.[12,15–17] Carcinoid syndrome, presenting with flushing, diarrhoea, palpitations and asthma-like symptoms, is caused by serotonin release from the tumour. Unlike its counterparts in the gut, classic carcinoid syndrome is rare in BC and is generally associated with metastatic disease. In fact, it is seen at presentation in only in 0.7 % of adult patients with BC[24] and is reported very rarely in paediatric patients.[12,25]

Diagnosis and Imaging

Diagnosis may be delayed due to low clinical suspicion and to the atypical ways in which pulmonary carcinoid can present. Early diagnosis increases the likelihood of definitive management. It is hoped that an increased awareness of BC will result in earlier diagnosis and surgical resection with a good prognosis.[21]

Endoscopy plays a central role in the diagnosis and initial management of carcinoids, and a bronchial biopsy should be taken whenever possible. BC typically reveals as a smooth pink–reddish or yellow endobronchial mass often covered by intact mucosa.

In the past, major haemorrhage after biopsy was feared,[26] but in specialised centres with daily clinical practice, endobronchial biopsy of a carcinoid (despite historical dogma to the contrary)[27] significantly increases the diagnostic yield without adding morbidity or mortality.[16,24]

A careful endoscopic assessment is also of fundamental importance to determine the feasibility of surgery and to plan the best surgical treatment, with the main aim being trying to determine the feasibility of a bronchoplastic procedure. Moreover, in these central tumours obstructing the major bronchi, endoscopic debulking with or without laser allows physicians to look behind the tumour and evaluate its base of implant. It also permits physicians to treat airway obstruction and avoid recurrent pneumonia, which could irreversibly damage the lung parenchyma. Patients with a suspected BC should undergo a clinical evaluation. Blood tests include chromogranin A, NSE and serotonin. Urinary tests with 24-hour urinary excretion of

Figure 1: An Example of Upper Right Sleeve Lobectomy

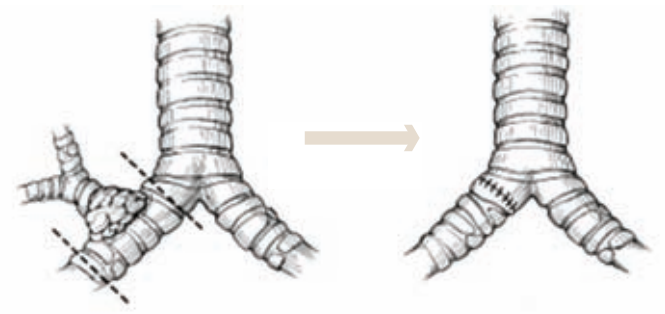
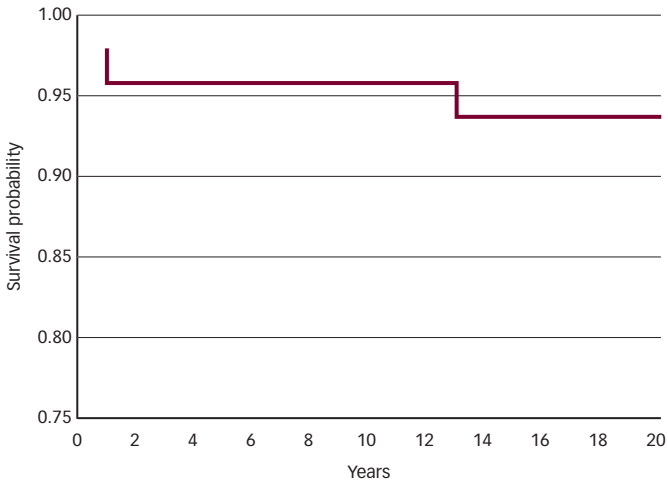


Figure 2: Disease-free Survival Probability Using a Meta-analysis Approach, Based on the Survival Reported by Four Major Studies[12,15,16,18]



5-hydroxyindolacetic acid (5-HIIA) are also indicated.[28] Radiological imaging remains an essential tool for the diagnosis and staging of BC in children. Chest X-ray often shows only obstructive pneumonia or atelectasis. Computed tomography (CT) of the chest with intravenous contrast enables the visualisation of extra-bronchial components to distinguish tumours from atelectasis and to stage disease, although node enlargement in the case of atelectasis is often a false-positive (20–40 %).[22] An ultrasound study of the upper abdomen is also recommended. Somatostatin receptor scintigraphy, also called an octereotide scan, can have a role in diagnostic practice in addition to CT. It can be useful in paediatric BC in peri-operative diagnosis in staging and also during follow-up to detect local recurrence or distant metastasis. It could be important to know the pre-surgical octreotide uptake, in particular in cases of recurrence, to programme radiolabelled somatostatin analogue therapy. The role of uorodeoxyglucose–positron-emission tomography (FDG-PET) scanning is more controversial: BCs in children are very often typical and have a low metabolic activity with a consequential low uptake at PET.

Management

Surgery represents the treatment of choice for pulmonary carcinoids, achieving long-term survival in cases of radical resection in both adults and children.[16,29,30] In young patients, when technically possible, lung-sparing resections should be performed; in these operations oncological results are similar to pneumonectomy but with a better quality of life and without skeletal problems related to growth.[30] Lung-sparing resections comprise bronchoplasty, wedge or sleeve resections of trachea or main bronchi or lobectomies associated with bronchial wedge or sleeve resection (see *Figure 1*). These procedures, which help to avoid resection of healthy respiratory tissue, sparing lobes or complete lung, have obvious advantages in children because of their long life expectancy.[27] In fact, pneumonectomy is a high-risk procedure correlated with a poor quality of life[31] and non-harmonic growth of the chest. In children airways are smaller and more delicate than in adults; therefore, paediatric experience and technical skill of the surgeon are of great importance to obtain the best result. Pneumonectomy has been reported for BC in children,[21,32–34] but fortunately in more recent years the use of pneumonectomy has declined.[12,16] Clean transaction lines, minimal handling of mucosa, avoidance of devascularisation and precise placement of the suture are the bases for successful bronchoplastic techniques,[27] keeping in mind that in BC the resection can be performed with free margins of only 1–2 mm without an increase in the local recurrence rate.[30]

The suture line can be covered with a pedicled flap of autologous tissue to reduce the potential risk of broncho-vascular fistula. The absence of mortality and post-operative complications and the excellent long-term survival in paediatric series support the use, when feasible, of sleeve resection and bronchoplastic procedures.[16,27,35]

Surgical resection of BC should be combined with lymph-node dissection. It is controversial whether a radical lymph-node dissection is necessary for BC or whether lymph-node sampling is enough. The prognostic relevance of lymph-node involvement in adult BC has been underlined by several authors,[29] but this is not yet established for children. Nevertheless, in our opinion systematic lymphadenectomy is justified due to the risk of lymph-node metastases (20 % at the time of surgery)[16] and the possibility of recurrence many years later in case of sampling.[16,36]

Laser treatment is not considered curative by many for two reasons: first, lymph-node dissection cannot be performed, and second, BC tends to spread extraluminally (iceberg phenomenon). Nevertheless, Cavaliere[37] reported good results in a very select group of adult patients treated only by laser therapy with radical intent. These patients had small typical BCs with a limited base implant and absence of lymph-node enlargement at CT scan. However, other authors[34] report two cases of pneumonectomy in children between 11 and 12 years of age that were necessary for bronchial recurrence after laser treatment two years previously. An extremely small number of cases could probably benefit from laser treatment alone, but it would be necessary to very carefully select patients and maintain a very close endoscopic follow-up (including bronchial biopsies) for many years.

Experience with chemotherapy or somatostatine analogue therapy to treat metastatic disease is discouraging in adults[11] and there is not enough experience in children to draw conclusions. The role of adjuvant radiotherapy in N2 disease is also debated and has not been proved to be beneficial. State-of-the-art radical surgical resection and lymphadenectomy remain the treatments of choice.

Histology, Prognosis and Survival

BCs have been classified in the spectrum of neuroendocrine lung tumours although they have a lower grade of malignancy than large- and small-cell carcinoma. TC and AC show similar pathological characteristics and biological markers, but the clinical behaviour

and prognosis are different. In adults TCs show a very favourable prognosis with a low local recurrence rate or distant metastases after radical resection, while ACs have demonstrated a poorer prognosis due to the higher oncological aggressiveness.[7,11,38–40]

Clinical behaviour is not as distinct between TCs and ACs in paediatric patients as it is in adults because of the limited number of cases.[15,17,34] Very few ACs are described in the literature in children[16,32,41] and, of these, two had lymph-node metastases at the time of surgery but neither recurrence nor reduced survival was observed.[16] Another presented mediastinal and cerebellar relapse 16 years later.[41] Despite being low-grade malignant tumours, BCs can spread to lymph nodes or distantly in paediatric patients too. The percentage of N^+ at the time of surgery in the major reports varies from 9 %[17] to 11.8 %[12] and then 20 %[16] (see *Table 1*), but it is difficult to define the prognostic value of nodal metastasis in a such a small population.

Diagnosis of metastatic BC in children is, fortunately, very rare,[25] but late local recurrences or distant metastases may occur many years after a radical surgery.[12,16,36] The reported rate of metastasis in children in historical reports is 5–27 %,[25,42,43] but these papers are not reliable because they could include bronchial adenomas and a recent histological revision has not been made.

When recurrence occurs, if technically possible, surgical treatment is recommended because it can probably prolong survival.[16,36]

From a meta-analysis approach, based on the survival reported by the four major studies (see *Table 1*), we can confirm that BCs in children, if promptly diagnosed and radically treated, have an excellent prognosis and a disease-free survival probability of 96 and 94 % at 10 and 20 years, respectively (see *Figure 2*).

Follow-up

Long-term follow-up is strongly recommended in BC. Despite low-grade malignancies, recurrences have been reported and their prompt diagnosis and treatment is important for long-term survival.

Prospective Future

Biological and molecular factors that influence the different behaviour of some carcinoid tumours have not been ascertained. There are tumours classified as TC with aggressive behaviour because they locally metastasise and have distant localisations. Various studies are in progress whose aim is to identify prognostic morphological and molecular markers that could help to define prognosis in TC and AC. Finding prognostic markers should allow the identification of TCs that are less aggressive and can benefit from endoscopic treatment. For the ACs with the worst prognosis, finding prognostic markers could lead to research for new specific drugs and biological treatments in the hope of obtaining better control over the disease. Future therapy of carcinoid tumours will be based on specific tumour biology, and treatment will be customised for each individual patient.

Conclusions

A BC tumour is an uncommon malignancy in paediatric patients. An early diagnosis is of fundamental importance because it allows prompt treatment. Operative bronchoscopy plays an important role in the diagnosis and treatment of obstruction, thus resolving symptoms, avoiding recurrent pneumonia, which could irreversibly damage the lung parenchyma and rule out a lung-sparing resection, and aiding in planning the correct operation. In experienced and skilled hands, conservative procedures with lymphadenectomy should be considered the treatment of choice for the management of paediatric BC, ensuring excellent survival and a good quality of life. A careful and prolonged follow-up is recommended. ■

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