



EXPeRT

**CARCINOMAS AND CARCINOID TUMORS OF THE
BRONCHI AND LUNGS IN CHILDREN AND
ADOLESCENTS**

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**STANDARD CLINICAL PRACTICE
RECOMMENDATIONS**

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TITLE: CARCINOMAS AND CARCINOID TUMORS OF THE BRONCHI AND LUNGS IN CHILDREN AND ADOLESCENTS

Document version: 1 (July 2025)

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Acknowledgments: Several authors of this publication are members of the European Reference Network on Pediatric Cancer (ERN PaedCan)

Funding: This publication has been supported by European Reference Network on Pediatric Cancer (ERN PaedCan), which is funded by the European Union within the EU4Health Programme 2021-2027 under the grant agreement number 101155946.

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1. Background and rationale

1.1.1 Summary

Even though neoplastic diseases are generally rare in childhood, some malignancies such as leukemias, lymphomas and central nervous system (CNS) tumors occur comparatively frequently. There is a very heterogeneous group of neoplasms that occur extremely rarely. Some of these tumors are typical for the pediatric age group, while others are very common tumors in adulthood, but only rarely develop in children and adolescents. These pediatric very rare tumors (VRT) are defined as “*any solid malignancy or borderline tumor characterized by an annual incidence < 2/million children < 18 years old*” according to the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) [1]. Due to the rarity of these tumors, it is almost impossible to conduct clinical trials for these tumor entities, which makes it difficult to establish evidence-based treatment recommendations. Therefore, the treatment of children and adolescents with VRT is often carried out on an individualized basis.

Background:

Primary lung malignancies in childhood are rare tumors, accounting for 0.2-0.5% of all pediatric cancers [2-4]. Carcinomas and carcinoid tumors of the bronchi and lung make up 50-70% of all pediatric primary lung malignancies [2, 4, 5]. These tumors mostly occur in adolescents with further increases in the rate of incidence into adulthood [5]. While typical, low-grade bronchial carcinoids and low-grade mucoepidermoid carcinomas are mostly localized with a favorable course, some patients with atypical bronchial carcinoids and especially patients with lung adenocarcinoma and squamous cell carcinoma, as well as rare cases of small-cell lung cancer, develop metastasis and carry a poor prognosis [5-7]. The rarity of these tumors in childhood and the non-specific nature of the presenting symptoms make it difficult to make a correct diagnosis in a timely manner. Considering the differing biological characteristics, both within the group of these tumor entities in childhood and in comparison to the corresponding tumors in adulthood with differing carcinogenesis, diagnostics and therapy need to be adapted to the pediatric age group. However, since these tumors rarely occur in childhood, there are no standardized recommendations for diagnosis and therapeutic management yet. While patients with localized tumors of low malignancy are adequately treated by complete resection, patients with metastatic disease require prompt multimodal therapy including systemic therapy (chemotherapy, immunotherapy, targeted therapies, radionuclide therapy), surgery, as well as focal radiotherapy in individual cases.

Objective:

To establish internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with carcinomas and carcinoid tumors of the bronchi and lung (“Standard of care recommendations for children with VRT”).

1.1.2 Background

While lung cancer is the second most frequent cancer type in both women and men in the US, the majority of cases occur in adults aged 50 years or older. In comparison, lung cancer in childhood is very rare [3]. In adulthood, 80-85% of lung cancer cases belong to the group of non-small cell lung cancer (NSCLC), which includes lung adenocarcinoma (LUAD), squamous-cell carcinoma, large cell carcinoma, as well as rare entities such as pleomorphic carcinoma, adenosquamous carcinoma (2-3%), while salivary-type cancer such as mucoepidermoid carcinoma (<1%, MEC) and adenoid cystic carcinoma is rare [8]. About 10-15% are cases of small-cell lung cancer (SCLC). Approximately 1-2% of all lung cancers are carcinoid tumors [9].

In contrast, in childhood, bronchial carcinoids (BC) are the most common lung malignancy accounting for 40-60% of pediatric primary lung tumors [4, 10]. Primary lung carcinomas have a proportion of approximately 20-25% of all primary lung malignancies in childhood, mainly NSCLC [4, 5]. Adenocarcinomas and mucoepidermoid carcinomas are the most common carcinoma subtypes in pediatric patients, while squamous cell and small cell lung carcinomas are very rare [4, 7]. Besides analyses of epidemiological cancer registries (partially up to the age of 20 years), there are several case series as well as case reports published on lung carcinomas and bronchial carcinoids at this age [6, 7, 11-23].

Notably, in children, other primary pleuropulmonary malignancies are also rare. Pleuropulmonary blastoma, frequently related to *DICER1* germline pathogenic variants, can occur in young children before the age of 5 years. Other malignant or borderline-malignant tumors are possible, such as thoracic inflammatory myofibroblastic tumors, pleural mesothelioma, NUT carcinoma, and sarcomas amongst others.

While the occurrence of lung cancer in adults is mainly associated with exogenous risk factors, the reasons for cancer development in childhood is largely unexplained. The significance of cancer predisposition syndromes has yet not been explored for BC, but such diseases associated with multiple endocrine neoplasia type 1 (MEN 1) have not been reported in childhood so far. While BC in adult patients show driver mutations in genes regulating histone modification and chromatin remodeling, pediatric BC have yet not been characterized by molecular genetics [24]. Pre-existing lung lesions such as congenital pulmonary airway malformation (CPAM) or human papilloma virus (HPV)-associated chronic laryngeal papillomatosis have been associated with primary lung carcinomas in childhood, occurring in up to 20% of cases [7, 25, 26].

In mucoepidermoid carcinoma in pediatric patients, predominantly somatic *MAML2* rearrangements were detected, which is more frequent than in adult mucoepidermoid carcinomas, but data on this is probably biased in adults due to inclusion of adenosquamous (mucoepidermoid-like) carcinomas that are now known to lack *MAML2* fusions [7]. Mucinous adenocarcinoma based on CPAM especially in infancy and early childhood seems to be a distinct clinical entity with canonical somatic *KRAS* mutation and generally favorable outcome [14]. Apart from this entity, primary lung carcinomas in children have not yet been systematically characterized with regard to their molecular biology, except for individual reports on *ALK*, *KRAS* and *ROS1* alterations [7, 11].

BC tumors are mainly located in the lobar bronchi, whereas in adult patients these tumors occur more peripherally [6, 27]. Lymph node metastases are found in 15-30% of cases and mainly occur in atypical BC in childhood [6, 15]. Distant metastatic spread is rarely observed in pediatric patients with BC and also associated with atypical histology [6].

Similarly, regional lymph node involvement is not common in pediatric mucoepidermoid carcinoma of the bronchi (10%), and distant metastases are extremely rare, in contrast to the slightly more commonly observed lymph node and distant metastases in adult mucoepidermoid carcinoma [7, 28]. In contrast, pediatric patients with lung adenocarcinoma, squamous cell carcinoma and rare cases of small-cell lung cancer mostly present with metastatic disease [2, 7].

While the goal is complete resection for all localized lung carcinomas and bronchial carcinoids, the extent of resection required in pediatric patients is not yet clearly defined (e.g. sleeve/sublobar resection, lymph node sampling/dissection) as well as the size of free margins [6, 7, 17, 29-31]. Pediatric patients with metastatic disease typically receive systemic therapies in a non-uniform manner, usually adapted from treatment recommendations for the corresponding adult tumors.

Pediatric patients with mucoepidermoid carcinomas of the lung and bronchial carcinoids have a very good outcome with a 10-year survival rate of between 90 and 100% (with the subgroup of atypical BC showing a lower survival rate) [2, 7]. This outcome was superior to the reported outcomes of adult patients with corresponding tumor entities (MEC: 72% 10-year overall survival; BC: 88% 10-year disease-specific survival) [9, 13]. In contrast, pediatric patients with lung adenocarcinoma, squamous cell carcinoma, and rare cases of small cell lung cancer have a 5-year overall survival (OS) rate of about 25%, which is comparable to the survival data of adults with these tumors [2, 10]. However, it remains unclear whether this is at least partly due to suboptimal therapeutic management adopted from adults, which may not be fully appropriate for children due to biological differences.

Like other pediatric VRT, due to their low incidence, lung carcinomas and bronchial carcinoids in children and adolescents present diagnostic and therapeutic challenges for radiologists, pathologists, surgeons, as well as pediatric and medical oncologists due to the aforementioned differences of the tumor entities compared to the corresponding tumors in adulthood. Since specific standardized guidelines are lacking, management decisions are currently made at a case-by-case level.

Here, we present the internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with carcinomas and carcinoid tumors of the bronchi and lung established by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT).

Important note: These recommendations are primarily for bronchial carcinoids (neuroendocrine tumors), salivary-type lung cancer and non-small cell lung cancer. Since data on neuroendocrine carcinomas (including small cell lung cancer) are extremely rare in children, no recommendations can be given for these entities.

2. Methodology

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from levels of evidence I to V and grades of recommendation A to E (Table 1) [32, 33].

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

It is noted by the EXPeRT group that due to the rarity of these tumors, no evidence of Level I to II exists. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the “strength” of recommendations will be categorized by additional grading (Grade A to E).

To identify tumors that need shared recommendations, EXPeRT members designed the following procedure:

- Identification of the tumor of interest on the base of its relevance, and previous EXPeRT experience (i.e., data analysis and publication). Tumors should be classified as VRT (i.e. < 2/1,000,000

inhabitants per year), not already analyzed in previous Expo-r-Net/ERN projects, not included in specific international protocols and frequent enough to be of interest [1].

- Designation of main coordinators for each VRT based on their experience (data analysis, publications, personal experience).

Coordinators must:

- Analyze the medical literature and select the relevant papers.
- Propose a series of recommendations in a form of a first draft of recommendations.
- Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, within the group of selected EXPeRT members and annotated.
- A refined version of the recommendations will be prepared, considering the suggestions of the group of selected EXPeRT members.
- The annotated draft will be then proposed to external experts identified by the coordinators based on a recognized experience on the tumor (pathologist, pediatric oncologist, medical oncologist, radiation oncologist, surgeon, ...).
- The final version will be validated by the whole EXPeRT group. In case of persistent differing assessments, a vote is taken during a physical and/or virtual consensus meeting to reach a final consensus.
- the approved and validated version will be available on SIOPE and EXPeRT websites and proposed for publication in an international peer review journal.

The final document including recommendations will be available on EXPeRT website.

NB: These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of their patients. The EXPeRT members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members of these groups via the ERN CPMS website: [CMPS 2.0](#)

3. Patient group

3.3.1 Diagnostic Criteria

Lung carcinomas and bronchial carcinoids may occur at any age. While BC in childhood are mainly reported in the adolescent age, the median age at diagnosis for these malignancies is about 60 years [6, 34]. Occurrence before the age of 10 years is exceptionally rare, but cases as young as 3 years of age have been reported [35]. Mucoepidermoid carcinomas in children are detected at a lower age (median 10.0 years, range 3.5-15.5) than LUAD and squamous cell carcinoma (SCC), which occur mainly in adolescence [7, 11]. However, it is noteworthy that especially mucinous adenocarcinoma arise in the context of a CPAM can appear as early as infancy and early childhood [14]. A balanced gender distribution is reported [10]. Presenting symptoms are usually of unspecific nature, such as cough, dyspnea, stridor, pain and further symptoms caused by inflammation, such as fever (regardless of the entity), and often resemble the symptoms of common chronic respiratory infection [6, 7, 11, 20, 21, 36]. In addition, there may be “true” pneumonia in the sense of post-obstructive infections. Due to the different age of onset for the different lung malignancies, further diagnostics should be performed regardless of age and sex if respiratory infection symptoms persist for more than 2-4 weeks after the onset of symptoms, depending on the general clinical condition and age of the patient. Additional factors that should prompt early diagnostic investigation are hemoptysis, additional symptoms such as weight loss and night sweats, known structural malformations of the bronchi or lung such as CPAM, lack of clinical response to antibiotic treatment for suspected bacterial pneumonia, and recurrent pneumonia in the same anatomical lung segment or lobe [6, 7]. The primary tumor is usually located in the bronchi/lungs, but can also spread to the parietal pleura, mediastinum and/or diaphragm [7]. In the case of distant metastasis, metastases are most commonly found in the contralateral lung, bones and central nervous system, and somewhat less frequently in distant lymph nodes or the liver [6, 7]. Malignant effusions, particularly in the pleura, can also occur [7]. Details are provided in Supplemental Table 1.

Multidisciplinary team (MDT) discussion should occur early in the assessment process of a pulmonary mass, preferably prior to any invasive procedure (including biopsy) and at all times of medical decisions. [Level V; Grade A]

3.3.2 Clinical evaluation and laboratory assessment

A complete history including concomitant diseases and weight loss must be recorded. Smoking and passive smoking should be considered. [Level IV; Grade B]

In addition, as part of the clinical history, attention should be paid to signs of carcinoid syndrome such as ectopic hormone production (including amenorrhea), structural lung diseases and malformations, as well as an increased incidence of cancer in the family (e.g. analogous to the Jongmans criteria; BC: MEN1 syndrome) [37, 38]. If the corresponding criteria are met, germline genetic counselling should be recommended to evaluate a possible cancer predisposition. [Level IV; Grade B]

A full clinical examination is mandatory, in particular to assess the general condition, weight, height, respiratory symptoms, clinical signs of ectopic hormone production (especially ACTH leading to Cushing's syndrome including hirsutism) and cervical and axillar lymph node status. [Level V; Grade A]

In the context of laboratory diagnostics, parameters for the assessment of inflammation and tumor-related organ insufficiencies/sequelae should be obtained: complete blood count with hemoglobin level, C-reactive protein, erythrocyte sedimentation rate (nonspecific), lactate dehydrogenase, liver and kidney function parameters (especially bilirubin, ALT, AST, creatinine, urea), bone profile (calcium, phosphate, and alkaline phosphatase) [39-42]. [Level V; Grade B]

Coagulation parameters (e.g. INR, aPTT) should be determined prior to interventions in case of conspicuous findings in bleeding assessment tools (e.g. ISTH/SSC questionnaire) [43]. [Level V; Grade A]

The following serum tumor markers and laboratory parameters suggestive for a tumor entity may be determined, especially if the respective entity is considered as differential diagnosis, including assessment of the relevance of the test in follow-up (it should be noted that a negative result does not completely rule out the corresponding tumor entity) [6, 39, 40, 44, 45]: [Level V; Grade C]

- Chromogranin A, Neuron-specific enolase (NSE), 5-hydroxyindoleacetic acid (5-HIAA, in 24h urine), Cortisol and ACTH (serum), Free Cortisol in 24h urine, GHRH and IGF-1 (serum) → BC, rarely small cell lung cancer; depending on symptoms of carcinoid syndrome, Cushing's syndrome or acromegaly mainly

- Possible, but not generally recommended:
 - Carcinoembryonic antigen (CEA), CA-125 → mainly LUAD
 - Cytokeratin 19 fragment (CYFRA 21-1), squamous cell carcinoma antigen → mainly SCC

3.3.3 Imaging

3.3.3.1 Primary tumor and its loco-regional tumor extension:

- Due to its widespread availability, rapid performance and low radiation exposure, a chest X ray (frontal and lateral view) remains the most common initial diagnostic test. [Level V; Grade B]
When interpreting the results, however, it is very important to note that, while the findings can often be helpful, they are mostly neither specific for the presence of a tumor nor for a particular entity. Pathological findings in the presence of bronchial/lung tumors can include abrupt truncation of bronchi, post-obstructive pneumonic infiltrates, atelectasis and other ventilation disorders, effusions, and mass lesions [46]. Mass lesions of BC and MEC are often located in the hilar or perihilar region and have a round to oval shape, rarely with calcifications [46, 47]. While a mass lesion consequently leads to further imaging diagnostics, especially smaller endobronchial mass lesions may not be visible on radiographs and mass lesions may be

masked by inflammatory processes. Since many of the abnormalities mentioned can be attributed to more common diagnoses, such as airway infections, it is essential to consider the findings in the context of the symptoms, duration of symptoms, and laboratory findings, and to perform a cross-sectional imaging if the differential diagnosis of a pulmonary malignancy persists. Likewise, persistent radiographic abnormalities along with clinical symptoms should lead to the consideration of endobronchial obstruction and further diagnostic evaluation, e.g. by cross-sectional imaging and/or bronchoscopy [48].

- A contrast-enhanced chest computed tomography (CT) must be conducted as cross-sectional imaging despite exposure to ionizing radiation [42, 46, 49]. [Level V; Grade A]. It allows the study of all components of the thorax with multiplanar reformation and a good spatial resolution. Intravenous contrast injection enables better characterization of tumor and better visualization of its mediastinal extension and the presence of lymph node involvement.

The location of the primary tumor and characteristics such as its relationship to the bronchial wall/lumen and calcifications can provide clues to the underlying entity. BC are usually partially endobronchial with a smaller intraluminal and a more substantial lung portion, which usually do not show calcifications – however, calcifications can rarely occur (in BC and also in MEC) [46, 50]. BC may demonstrate intense enhancement due to vascularization [51]. Bronchiectasis filled with mucus can occur due to recurrent infection/inflammation. Similar characteristics have been described for mucoepidermoid carcinoma [46, 52]. LUAD and SCC usually present as a mass or nodule with a predominantly solid component, or as a mass-like consolidation with associated signs resembling pneumonia [46]. There may be associated findings such as local invasion of the pleura, chest wall, or diaphragm. In addition, this examination helps to detect enlarged hilar and mediastinal lymph nodes. However, due to the common presentation of tumor-associated lung infection, the interpretation of imaging is sometimes difficult, especially with regard to thoracic lymph node involvement. In these cases, follow-up imaging after antibiotic treatment may be considered. In selected cases with unclear regional lymph node involvement, [18F]FDG-PET/CT or [18F]FDG-PET/MRI are further diagnostic options.

- Magnetic resonance imaging (MRI) of the chest with contrast may be conducted in individual cases to assess specific aspects (especially with regard to soft tissue) or if exposure to radiation should be avoided under any circumstances. However, MRI-based imaging of lung lesions is currently often still inferior to CT [46]. MRI may be useful for staging and, in particular, for differentiating between reactive and tumoral lymph nodes. [Level V; Grade C]
- Somatostatin receptor (SSTR) imaging (SSTR-directed PET imaging or, if not available, Octreoscan) may be discussed when suspecting a carcinoid tumor to differentiate BC from other histological types of lung cancer, to avoid biopsy before surgery (especially if the tumor is too peripheral to be biopsied by endoscopy) and to identify metastases, but the role is uncertain as no data exist in children [53]. [Level V; Grade C]

3.3.3.2 Distant metastasis

The initial staging evaluation, especially for suspected LUAD and SCC, must be systematically comprehensive because diagnosis often coincides with metastatic disease. Once the diagnosis is established, it must include a chest CT scan for detecting ipsilateral or contralateral involvement of the lungs. [Level V; Grade A]

Additionally:

- Pediatric Patients with BC:
 - o Following the ESMO recommendations for adults with BC, an abdominal MRI including late-phase liver imaging for assessment of liver metastases may be performed [6, 49]. [Level V; Grade C] In case of typical BC, an ultrasound of the abdomen may be performed alternatively. [Level V; Grade C]
 - o Additional [18F]PET/CT imaging with ⁶⁸Ga-DOTA-conjugated somatostatin receptor targeting peptides should be conducted at least in cases of BC with suspected lymph node metastases and/or distant metastases [6, 49, 54] [Level V; Grade B]. In all other cases, somatostatin receptor imaging may be discussed individually, especially in cases of atypical BC even without suspected metastases. [Level V; Grade C]
- Pediatric Patients with NSCLC and MEC:
 - o As MEC in childhood are usually low-grade malignancies without distant metastases, we propose to refrain from performing a whole-body [18F]FDG-PET imaging on these patients if there is no hint on regional lymph node involvement. [Level V; Grade D]
 - o ¹⁸F-fluorodeoxyglucose positron emission tomography/CT ([18F]FDG-PET/CT) is recommended in the adult guidelines for patients with NSCLC and possible (oligo-) metastatic disease or suspected bone metastasis [42]. The value of whole-body [18F]FDG-PET/MRI is not defined yet.
 - o We propose to perform whole-body [18F]FDG-PET imaging in pediatric patients with Non-MEC primary lung carcinoma. In the adolescent age group, this should be primarily conducted as [18F]FDG-PET/CT. [Level V; Grade B] Whole-body [18F]FDG-PET/MRI may be considered in young children with Non-MEC primary lung carcinoma. [Level V; Grade C]
 - o Depending on the clinical presentation, initial symptoms and localization of metastases, further investigations should be considered, in particular a contrast-enhanced MRI of the brain in the presence of neurological signs / metastatic disease or transthoracic echocardiography in case of carcinoid syndrome [42]. [Level V; Grade B]

Staging should be conducted according to the TNM classification for lung cancer by the American Joint Committee on Cancer (AJCC; Supplemental Table 2) [55]. [Level IV; Grade B]

3.3.4 Biopsy/Histopathology

When lung carcinomas and bronchial carcinoids are suspected - based on clinical and radiological findings - histology must be obtained [5]. [Level IV; Grade A]

Biopsy

In case of primarily unresectable tumor or metastasized disease, a biopsy of the primary or a distant site is mandatory [56]. [Level V; Grade A] In the case of a completely resectable tumor, biopsy before definitive resection may be considered.

In most cases, biopsy of the primary site is performed either via bronchoscopic technique (bronchial primary tumor), (image-guided) biopsy through resection of a metastatic mass (e.g. lymph node; preferred in metastatic disease), CT scan or ultrasound-guided transthoracic biopsy (on the primary or on metastatic sites), mediastinoscopy, or via guidance by endobronchial endoscopic ultrasound [42, 49]. [Level V; Grade B]

It must be noted that the amount of material obtained in bronchoscopic biopsy may not be sufficient to differentiate between sub-types of lung cancer, particularly between typical and atypical BC [6, 49]. However, efforts should be made to ensure that sufficient material is available for molecular testing including next generation sequencing (NGS), especially in the case of suspected LUAD or SCC. The endoscopic picture of BC is quite characteristic, with an endobronchial berry-like vegetation that easily bleeds on contact with the endoscope. In this case, biopsy of the lesion must be performed cautiously because of the possibility of bleeding, if indicated (in case of primarily unresectable tumor or metastasized disease).

Endosonography may be conducted for patients with abnormal mediastinal and/or hilar lymph nodes on imaging, and pathological confirmation of suspected lymph node involvement should be sought by ultrasound-guided needle aspiration (alternatively, mediastinoscopy) [57]. [Level V; Grade B]

Histopathology

A reference national or international pathology review in addition to the local pathological analysis is recommended for all pediatric primary lung malignancies. [Level V; Grade B] Histopathological diagnosis is made according to the current guidelines by the World Health Organization (WHO) classification [58, 59]. It must be noted that the following assessments are primarily based on adult data.

BC are well-differentiated tumors that can be divided into typical low-grade BC (<2 mitoses/2 mm², no necrosis) and atypical intermediate-grade BC (2–10 mitoses/2 mm² and/or foci of punctate necrosis), with the latter more likely to metastasize [58]. Although not used as a classification criterion, the Ki-67 index can be useful in the distinction between BC and poorly differentiated tumors [60]. Reported values are commonly <5% in typical BC and <20% in atypical BC [49, 61, 62]. An overlap in Ki-67 index levels between typical BC and atypical BC has been reported [49]. The best combination for identifying neuroendocrine tumors via immunohistochemistry is a panel of chromogranin A, synaptophysin, and

INSM1 [60]. The pneumocyte marker TTF1 is variably expressed by BC but may be negative in low-grade tumors [49].

MEC are composed of a heterogeneous mixture of mucin-secreting, squamoid/epidermoid, and intermediate cells. Tumor cells of MEC are usually negative for TTF1, Napsin A, positive for cytokeratins and variably positive for CK5/6 and p63/p40 [13, 36, 63]. *MAML2* gene rearrangement, which is a defining feature frequently found in MEC, can be examined (e.g. by FISH, NGS, transcriptome) to distinguish them from adenosquamous carcinomas [7, 63].

In LUAD, TTF1 and Napsin A staining are positive in most cases [60]. The simultaneous positivity of TTF1 and CK7 in the same tumor usually indicates LUAD and is considered as the gold standard for diagnosis [60]. LUAD and SCC are usually distinguished by evaluating TTF1 (LUAD mostly positive; SCC typically negative) and p63/p40 (SCC typically diffusely positive; LUAD negative); if these two markers do not allow a clear distinction to be made, CK5/6 (SCC is typically positive) enables the distinction between these subtypes. [64].

A programmed death-ligand 1 (PD-L1) immunohistochemistry analysis is recommended for all stage II-IV NSCLC cases with the exemption of salivary-type carcinomas such as MEC [42].

Histopathological reports should include information regarding grading as well as proliferation indices. In case of NSCLC, HER2 expression should be reported. The presence of a NUT carcinoma (*NUTM1* rearrangement) should be ruled out by immunochemistry (or molecular analysis) if this is a differential diagnosis based on histopathological review [65].

3.3.5 Molecular pathology / Analysis of potential therapeutic targets

The inclusion of patient material for molecular genetic diagnostics in the context of research projects is highly recommended. Somatic molecular genetic diagnostics at initial diagnosis (predictive testing) are generally not recommended for localized, resectable low-grade MEC (besides *MAML2* rearrangement) or BC. [Level V; Grade D]

In the case of unresectable high-grade MEC or BC or in the presence of distant metastases, molecular genetic diagnostics should be considered to evaluate the possibility of targeted therapies. [Level V; Grade B] For non-MEC lung carcinomas, molecular genetic analysis should be conducted in all stage II, III and IV cases [7]. [Level V; Grade B] This can be performed as a panel of targetable alterations or exome/genome plus transcriptome sequencing from tumor material, depending on availability [7, 14, 66-69]. In general, NGS of tumor DNA and RNA is preferred over other methods for detecting genetic alterations, if available [56, 70, 71].

Analogous to treatment-relevant alterations in adult NSCLC, at least the following molecular alterations should be determined as defined in the current ESMO guidelines [56]: [Level V; Grade B]

- *EGFR* mutations (especially in exons 18-21, including p.T790M testing regarding resistance) [7, 11]
- *ALK* rearrangements (standard: immunohistochemistry; FISH; transcriptome) [7, 11, 71, 72]
- *ROS1* rearrangements (standard: immunohistochemistry; FISH; transcriptome) [11, 71]

-
- *BRAF* p.V600X mutation
 - *NTRK* rearrangements (immunohistochemistry; transcriptome)
 - *MET* exon 14 skipping mutations
 - *MET* amplifications
 - *RET* rearrangements
 - *KRAS* p.G12C mutations
 - *HER2* mutations
 - *HER2* amplification (and overexpression)

Since the molecular alterations in these tumors are not well characterized in children, it should be considered to also analyze targetable alterations beyond those relevant for therapy in adult patients.

3.3.6 Additional assessments

- Before chemotherapy, **laboratory work-up** (full blood count, liver and renal function tests) and **specific evaluations** depending on chemotherapeutic agents delivered (e.g., audiometry, echocardiography) are required. [Level V; Grade A]
- An **echocardiography** should be conducted at least in BC to rule out carcinoid heart disease [Level V; Grade B]
- For other thoracic tumors, prior to any extensive surgery, **pulmonary function tests and cardiac specific evaluations** may be required, especially depending on the organs included in the irradiation fields such as echocardiography. [Level V; Grade B]
- **Fertility preservation options** must be considered before medical therapy [Level V; Grade A]
- In case of a stage IV NSCLC and MEC, **pediatric palliative care specialists** should be involved at diagnosis in the MDT discussions. [Level V; Grade B]

A summary of characteristic features of distinct carcinomas and carcinoid tumors of the bronchi and lung in pediatric patients is displayed in Supplemental Table 1.

A flowchart illustrating the proposed core diagnostic approach for pediatric patients with suspicion of carcinomas and carcinoid tumors of the bronchi and lung is displayed in Supplemental Figure 1.

4. Treatment details

4.1.1 General considerations

- **MDT** consultation including medical oncologists specialized in adult lung carcinomas is mandatory at diagnosis and during therapy. [Level IV; Grade A]
- **Psychosocial support** must be offered at diagnosis and during therapy and follow-up. [Level IV; Grade A]

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- Patients/families should be invited to participate in a **prospective clinical trial** when available, with **data collection** in national or international registries to improve the knowledge of these diseases. [Level V; Grade B]
 - Patients/families should be invited to participate in **molecular analyses/biobanking projects** when available. [Level V; Grade B]
 - For BC: before any invasive therapeutic procedure, the **control of a potential clinical carcinoid syndrome** must be ensured. [Level V; Grade A]

Flow charts of the proposed therapeutic approaches for the distinct tumor entities in childhood are displayed in Supplemental Figures 2-4.

4.1.2 Surgery

Prior to surgical interventions, an ECG and respiratory function tests may be performed. [Level V; Grade C]

Surgery may be carried out upfront after adequate medical preparation in localized resectable tumors resembling BC or MEC or in tumors considered at high risk of bleeding [7]. [Level V; Grade C]

The approach to surgical intervention depends on the entity and extent of disease:

- NSCLC / MEC
 - Complete surgical resection is recommended in all patients with locoregional disease and, if present on imaging, resectable lymph node metastases [5, 7, 12, 20, 57]. [Level IV; Grade A] The aim is to obtain a microscopically complete resection (R0). In general, anatomical resections (e.g. lobectomy, segmentectomy) are considered as standard treatment [11, 12, 36, 57]. [Level IV; Grade A] In case of low-grade NSCLC / MEC as well as small tumors (<2 cm), tissue-sparing non-anatomical resections such as wedge or sleeve resections (potentially using frozen section examination during surgery if locally possible) should be performed by experienced surgeons provided that a complete resection with free margins (R0) can thereby be achieved [5, 12, 36, 70]. [Level V; Grade A] Resection may be performed via open thoracotomy or video-assisted thoracoscopic surgery based on the expertise of the surgeon. [Level V; Grade B]
 - Regional lymph node resection should be conducted according to the International Association for the Study of Lung Cancer Lymph Node Map for staging purposes [36, 73]. Respective lymph node dissection has been associated with a superior survival in case of regional or distant metastases [5]. [Level V; Grade B] If a diagnosis of a low-grade MEC has been made prior to resection, regional lymph node resection may be limited to initially enlarged lymph nodes on imaging [Level V; Grade C] Complete resection is also recommended for patients with multifocal lung cancer, whenever possible [5, 20]. [Level V; Grade B]

In intermediate- and high-grade tumors with lymph node involvement (N1/N2) surgery should be incorporated in a multimodal treatment approved by the MDT [57].

- In case of incomplete resection (microscopically R1/macrosopically R2), an immediate re-resection should be discussed considering the possibility of a microscopically complete resection, the sequelae as well as the tumor type and grading. [Level V; Grade B]

In case of a low-/intermediate grade MEC and resection with microscopic residues (R1) of the primary and complete resection of potentially affected lymph nodes, a re-resection may not be systematically necessary. [Level V; Grade C]

- In case of oligometastatic disease, a multimodal focal treatment including local radical therapy/resection/thermal ablation/stereotactic radiotherapy with curative intention may be evaluated in the MDT. [Level V; Grade C]
- In case of unresectable lymph node involvement and/or unresectable distant metastases and/or poly-metastatic disease, multimodal treatment with medical therapy should be aimed at [7]. [Level V; Grade B]
- In patients with stage II/III disease, neoadjuvant treatment may be considered (as described in 'Chemotherapy and Immunotherapy' chapter) [Level V; Grade C]
- No statistical survival benefit for children with stage IV disease undergoing iterative surgical interventions has been proven, however, a trend towards a better survival has been noted [5]. [Level V; Grade C]

- BC

- Complete resection is recommended in all patients with localized resectable disease [5, 6, 17, 20, 23, 29, 49]. [Level IV; Grade A]

Anatomical resections (primarily lobectomy, segmentectomy, bi-lobectomy) and lung parenchyma-sparing resections (sleeve resections) should be conducted based on the localization and size of the tumor lesion(s) [6, 15, 17, 29, 35]. [Level IV; Grade B]

While tumors in peripheral localization may be treated with anatomical resection, bronchoplastic surgery such as sleeve resections (potentially using frozen section examination during surgery) should be evaluated by experienced surgeons for centrally located tumors to avoid pneumonectomy [17, 29, 49]. [Level IV; Grade B]

Bronchoscopic resections may be evaluated based on localization of the tumor and probability of a complete resection, primarily for centrally located and low-grade tumors to avoid extensive resections of lung tissue [23, 29, 74]. [Level V; Grade C]

Regional lymph node resection should be conducted according to the International Association for the Study of Lung Cancer Lymph Node Map for staging purposes in all patients systematically with initially enlarged lymph nodes on imaging [Level V; Grade B] and may be discussed in the other patients [17, 21, 73]. [Level V; Grade C]

- In case of incomplete resection, a re-resection should be evaluated. [Level V; Grade B] In case of typical BC and R1 resection of the primary and complete resection of

potentially affected lymph nodes, the MDT should discuss the need for re-resection, considering the associated morbidity; adjuvant therapy may not be necessary. [Level V; Grade C]

- In case of oligometastatic disease, a multimodal treatment including local radical therapy/resection with curative intention should be evaluated in the MDT. [Level V; Grade B]
- Liver metastases may be treated if curative intent is pursued; options include surgery, thermoablation, and stereotactic radiotherapy [6, 29]. [Level V; Grade C]
- In case of unresectable lymph node involvement and/or unresectable distant metastases and/or poly-metastatic disease, multimodal treatment should be aimed at. [Level V; Grade B]

For all entities, minimally-invasive approaches using both standard thoracoscopy (VATS, video-assisted thoracoscopic surgery) and robotic surgery (RATS, robot-assisted thoracoscopic surgery) may be appropriate and suitable for selected patients. Patient selection should be based not only on patient-related or tumor-related criteria (e.g., age, weight, tumor size, local invasiveness), but also on the center's expertise in both pediatric oncological surgery and minimally-invasive surgery to ensure both safety and a good oncological outcome. [Level V; Grade C]

4.1.3 Radiotherapy

- NSCLC/MEC
 - Postoperative radiotherapy should be considered besides evaluating re-resection in the MDT in case of a resection with microscopic residues (R1) of a NSCLC [57]. [Level V; Grade B] Postoperative radiotherapy may be discussed besides evaluating re-resection in the MDT in case of a resection with microscopic residues (R1) of a high-grade MEC [Level V; Grade C]
 - If there is an indication for adjuvant chemotherapy (e.g. due to metastatic spread), radiotherapy should be applied after chemotherapy. [Level V; Grade B]
 - In case of unresectable locoregional NSCLC, a concurrent radio-chemotherapy may be considered based on the adult NSCLC guidelines (up to 60–66 Gy in 30–33 daily fractions) [57]. [Level V; Grade C]
 - In case of stage IV NSCLC, radiotherapy may be applied for symptom control (e.g. irradiation on the primary tumor or bone metastases) [7, 20, 42]. [Level V; Grade C]
- BC
 - Postoperative radiotherapy may be considered in patients with atypical BC and lymph node involvement in the MDT [20, 49]. However, in case of complete resection (including affected lymph nodes) an observation may be opted for. [Level V; Grade C]

- In patients with BC and metastatic disease, SSTR-directed peptide receptor radionuclide therapy may be considered in the MDT in case of receptor-positive disease [29, 49]. [Level V; Grade C]
- In case of metastasized BC, focal conventional radiotherapy on metastatic sites may be applied for symptom control (e.g. irradiation of bone metastases) [6] [Level V; Grade C]

4.1.4 Chemotherapy and Immunotherapy

- NSCLC:
 - In patients without targetable *EGFR* mutation or *ALK* rearrangement in stage II to IIIB (resectable tumors deemed at high risk of recurrence), neoadjuvant treatment with 3 cycles of immunochemotherapy in case of PD-L1 positivity ($\geq 1\%$) should be considered, as a corresponding approach is established for adults [Level V; Grade B]
 - In analogy to the adult guidelines, adjuvant medical therapy is recommended for patients with stage II or III disease after complete resection [7, 11, 57]. [Level V; Grade A]

For patients with stage IB disease, adjuvant chemotherapy may be considered on an individual basis. [Level V; Grade C]

A two-drug chemotherapy including cisplatin (e.g. cisplatin + vinorelbine) is proposed for 3-4 cycles in line with the treatment of adults for patients to whom the following constellations do not apply [7, 11, 57] [Level V; Grade C] :

Anti-PD(L)-1 checkpoint inhibition may be discussed on an individual basis for stage II/III NSCLC according to pathology pattern. [Level V; Grade C]

In patients with stage II or III disease and proven targetable rearrangements in *ALK* or *ROS1* as well as targetable mutations in *EGFR*, respective targeted treatment should be discussed instead of chemotherapy. [Level V; Grade C]

- For unresectable stage III disease, a concurrent radio-chemotherapy including 2-4 cycles of cisplatin-based chemotherapy (+ vinorelbine, or etoposide, or paclitaxel, or - in case of non-squamous histology - gemcitabine) is recommended in adult guidelines [57]. In pediatric patients with unresectable stage III disease, this treatment option may be evaluated in the MDT together with further potential treatment options (including potential targetable somatic alterations, similar to stage IV disease). [Level V; Grade C] Although the use of durvalumab for 12 months is recommended for adult patients after the radiochemotherapy phase, provided there is no progression and no contraindications, there are no corresponding data for pediatric patients. Therefore, such an approach should be discussed individually in the MDT with the involvement of

adult oncologists. [Level V; Grade C]

- Patients with metastatic disease and without clearly treatment-relevant somatic targetable alterations (as specified in 4.1.5) must usually receive a combination treatment of conventional chemotherapy and anti-PD-(L1) inhibition regardless of the PD-L1 status [7, 11, 42]. [Level IV; Grade A] (E.g. platinum, pemetrexed and pembrolizumab for non-squamous NSCLC; carboplatin, (nab)-paclitaxel and pembrolizumab for squamous-cell carcinoma [42]). However, the individual treatment approach should be discussed in the MDT together with other treatment options (e.g. nivolumab + ipilimumab + chemotherapy) [7, 11, 42]. [Level V; Grade B]
- MEC:
 - There is little to no evidence for the efficacy of medical therapy in pediatric patients with MEC, since high-grade disease is rare [20]. Patients with low-/intermediate-grade MEC and complete resection need no further treatment [7]. [Level IV; Grade A] Patients with low-/intermediate-grade MEC and microscopically incomplete resection should be discussed in the MDT, primarily considering observation after surgery without any adjuvant therapy. [Level V; Grade B]
 - Patients with unresectable/metastatic MEC or with high-grade MEC should be discussed in the MDT, primarily considering medical therapy as well as focal therapies on metastatic sites. [Level V; Grade B] Treatment may follow the adult NSCLC guidelines [42]. [Level V; Grade C]
- BC
 - In case of typical BC and complete resection of the primary and complete resection of potentially affected lymph nodes, no adjuvant therapy is indicated. [Level V; Grade B] In case of typical BC and resection with microscopic residues (R1) of the primary and complete resection of potentially affected lymph nodes, adjuvant therapy may not be necessary. [Level V; Grade C]
 - Otherwise, no recommendations for routine adjuvant treatment can be given. [Level V; Grade C]
 - In case of metastatic and unresectable/progressive disease as well as atypical BC and lymph node involvement, the further treatment options besides peptide receptor radionuclide therapy may be discussed in the MDT with medical oncologists (analogous adult recommendations): [Level V; Grade C]
 - Everolimus treatment [6, 29]
 - Dacarbazine/temozolomide-based chemotherapy [6, 29, 49]
 - Platinum-based chemotherapy [29, 49]
 - Somatostatine analogues in case of slowly progressive BC with somatostatine-receptor-positive imaging [29]

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- IFN-alpha [29]

4.1.5 Targeted therapy

Besides stage IV NSCLC, the currently published European adult guidelines for NSCLC and BC do not yet recommend the application of targeted therapies [57]. However, in clinical practice, targeted treatments (mainly Osimertinib in case of *EGFR* mutation, Alectinib in case of *ALK* rearrangement) are already applied in adult patients with stage II-III NSCLC. Based on an individual risk-benefit-assessment of all potential therapeutic modalities, targeted therapies based on tumor sequencing may be complementary discussed in case of a microscopically incomplete resection, unresectable lymph node involvement or progressive disease in pediatric patients with stage II-III disease, ideally in a prospective protocol.

In case of metastatic NSCLC or MEC, targeted treatment in case of respective somatic alterations is recommended in analogy to the adult guidelines, although – besides *ALK* inhibition – there is practically no data on pediatric patients [56]. Targeted treatment includes the following alterations. (*ALK* [Level IV; Grade B]; all others: [Level V; Grade C])

- *ALK* rearrangement [7, 71, 72, 75-77]
- *EGFR* mutation
- *ROS1* rearrangement [71]
- *BRAF* V600 mutation
- *NTRK* rearrangements
- *MET* exon 14 skipping mutations
- *MET* amplifications (currently, there is no respective EMA/FDA approved treatment for adult patients, however, there are reports on targeted treatments in adults, e.g. with Capmatinib or Tepotinib)
- *RET* rearrangements
- *KRAS* G12C mutations
- *HER2* mutations
- *HER2* amplification and overexpression

Further targetable alterations in NSCLC and MEC may be discussed in a molecular tumor board as an additional treatment option [66, 67]. [Level V; Grade C]

For patients with metastatic BC, targetable alterations may be discussed in a molecular tumor board as an individualized treatment approach. [Level V; Grade C]

4.1.6 Treatment of relapse

In the event of a relapse or progression during therapy, the therapeutic strategy should also be discussed with medical oncologists. Discussion in a specialized tumor board (e.g. ERN PaedCan

CPMS) is also recommended. [Level V; Grade B] Re-operation remains a cornerstone for any tumor recurrence.

In principle, the approach is based on the guidelines for adults. Re-evaluation of new targetable somatic alterations or the occurrence of resistance should be conducted by re-sampling for extended molecular profiling. In particular, in the case of *ALK* rearrangements in NSCLC, a switch of *ALK* inhibitors can lead to a renewed and sustained response [7]. [Level V; Grade B]

5. Assessments

Patients should receive clinical and radiological evaluation before, during and after completion of treatment. In general, chest CT scans with contrast should be performed. In the case of initial metastatic disease, all known metastatic sites should be investigated using adequate imaging, e.g. PET-based re-assessment.

Response to chemotherapy should be evaluated every two cycles (or every 2–3 months), before surgery to plan the procedure and after surgery to assess possible residual tumors, before adjuvant chemotherapy, before radiotherapy to plan the irradiation, and after irradiation. [Level V; Grade B]

Further imaging investigations should be considered depending on the clinical assessment.

6. Genetic considerations

Besides genetic counselling based on the Jongmans criteria as stated in 3.3.2, germline genetic testing for *MEN1* mutations should be conducted for patients with BC in case of suspicion of a MEN1 syndrome [21, 29]. [Level V; Grade A]

7. Follow-up

- NSCLC / MEC
 - Stage I-III: follow-up including history, physical examination, and contrast-enhanced chest CT scan every 3 months for 2-3 years after end of treatment, then every 6 months until 5 years after end of treatment, then without routine imaging every 12 months until at least 10 years after end of treatment. Laboratory workup depending on the treatment received. [Level V; Grade C]
 - Stage IV: follow-up including history, physical examination, contrast-enhanced chest CT scan, and whole-body imaging depending on the location of metastases/initial imaging (MRI or [18F]FDG-PET/CT or [18F]FDG-PET/MRI) every 3 months for 5 years after end of treatment, then every 6-12 months until at least 10 years after end of treatment. Laboratory workup depending on the treatment received. [Level V; Grade C]

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- Ultrasound of the thyroid gland every 2 years and thyroid function (free T4, TSH) in case of neck irradiation. [Level V; Grade C]
 - Respiratory function tests every 1-2 years after thoracic surgery or radiotherapy. [Level V; Grade C]

 - BC
 - Completely resected, localized typical BC: follow-up including history, physical examination, laboratory testing (including serum chromogranin-A if preoperatively done and positive) without any routine CT scans every 6 months for the first 2 years and every 12 months thereafter until at least 10 years after end of treatment [6]. [Level V; Grade C]
 - Atypical BC, BC with resected metastases, BC after incomplete resection: follow-up including history, physical examination, laboratory testing (including serum chromogranin-A) every 3 months for the first 2 years, then every 6 months until 5 years after end of treatment, then every 12 months thereafter until at least 10 years after end of treatment. This should be complemented by chest CT scans and MRI scans (or ultrasound examinations) of the abdomen at 3, 6, and 12 months in the first year and every 6 months thereafter for a total of at least 2 years [6]. [Level V; Grade C]
Afterwards chest CT scans and chest X-ray might be performed alternately every year in metastatic and/or atypical BC.
In patients with atypical BC and/or resected metastases, SSTR-directed imaging should be considered at least once during follow-up (at 1 year after surgery). [Level V; Grade C]
 - Respiratory function tests every 1-2 years after thoracic surgery. [Level V; Grade C]

The follow-up recommendations are also summarized in Supplemental Table 3.

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9. Supplemental material

Supplemental Table 1. Summary of characteristic features of carcinomas and carcinoid tumors of the bronchi and lung in pediatric patients

Entity	Characteristic features in pediatric patients
Carcinoid tumor	<ul style="list-style-type: none"> • partially endobronchial and mainly hilar/perihilar localization • primarily adolescents • mostly small tumors (median size 2-3 cm) • immunohistochemistry: combination of chromogranin A, synaptophysin and INSM1 • majority with typical histology and rare regional/distant metastatic spread • atypical histology associated with increased risk of unfavorable courses • favorable prognosis
Mucoepidermoid carcinoma	<ul style="list-style-type: none"> • partially endobronchial and mainly hilar/perihilar localization • all age groups • mostly small tumors (median size 2 cm) • characteristic somatic <i>MAML2</i> rearrangement • mostly low-grade tumors • rare regional/distant metastatic spread • favorable prognosis
Adenocarcinoma	<ul style="list-style-type: none"> • mostly solid mass/mass-like consolidation in the lung parenchyma • primarily adolescents (besides mucinous adenocarcinoma in infancy/early childhood, associated with CPAM) • mostly larger tumors • immunohistochemistry: mostly TTF1 and CK7 positive • common regional/distant metastatic spread • rather unfavorable prognosis
Squamous cell carcinoma	<ul style="list-style-type: none"> • mostly solid mass/mass-like consolidation in the lung parenchyma • primarily adolescents • mostly larger tumors • immunohistochemistry: mostly p64/p40 positive, TTF1 negative • common regional/distant metastatic spread • rather unfavorable prognosis

Further diagnoses are not mentioned (e.g. adenosquamous carcinoma, small cell lung cancer) due to the extreme rarity and lack of respective data in pediatric patients.

Supplemental Table 2. TNM staging for lung carcinoma according to the American Joint Committee on Cancer (AJCC), 9th edition. [55]

Stage	T ¹	N ²	M ³
0	Tis	N0	M0
IA1	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
	T1a-c	N1	M0
IIB	T1a-c	N2a	M0
	T2a-b	N1	M0
	T3	N0	M0
IIIA	T1a-c	N2b	M0
	T2a-b, T3	N2a	M0
	T3, T4	N1	M0
	T4	N0	M0
IIIB	T1a-b, T2a-b	N3	M0
	T2a-b, T3, T4	N2b	M0
	T4	N2a	M0
IIIC	T3, T4	N3	M0
IVA	any T	any N	M1a, M1b
IVB	any T	any N	M1c1-2

¹ T component

- Tis Carcinoma in situ
- T1 Tumor surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus
 - T1a Tumor ≤1 cm in greatest dimension
 - T1b Tumor >1 cm but ≤2 cm in greatest dimension
 - T1c Tumor >2 cm but ≤3 cm in greatest dimension
- T2 Tumor with any of the following features:
 - T2a
 - tumor >3 cm but ≤4 cm in greatest dimension;
 - invades visceral pleura;

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- invades an adjacent lobe;
 - involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis extending to the hilar region, involving either part of or the entire lung
 - T2b Tumor >4 cm but ≤5 cm in greatest dimension
 - T3 Tumor with any of the following features:
 - tumor >5 cm but ≤7 cm in greatest dimension;
 - invades parietal pleura or chest wall;
 - invades pericardium, phrenic nerve, or azygos vein;
 - invades thoracic nerve roots (i e T1, T2) or stellate ganglion;
 - separate tumor nodule(s) in the same lobe as the primary
 - T4 Tumor with any of the following features:
 - tumor >7 cm in greatest dimension;
 - invades mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus or diaphragm;
 - invades heart, great vessels (aorta, superior/inferior vena cava, intrapericardial pulmonary arteries/veins), supra-aortic arteries, or brachiocephalic veins;
 - invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (i e trunks, divisions, cords, or terminal nerves);
 - separate tumor nodule(s) in a different ipsilateral lobe than that of the primary

² N component

- N0 No regional lymph node metastasis
- N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar and/or intrapulmonary lymph nodes, including involvement by direct extension
- N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
 - N2a – Single N2 station involvement
 - N2b – Multiple N2 station involvement
- N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

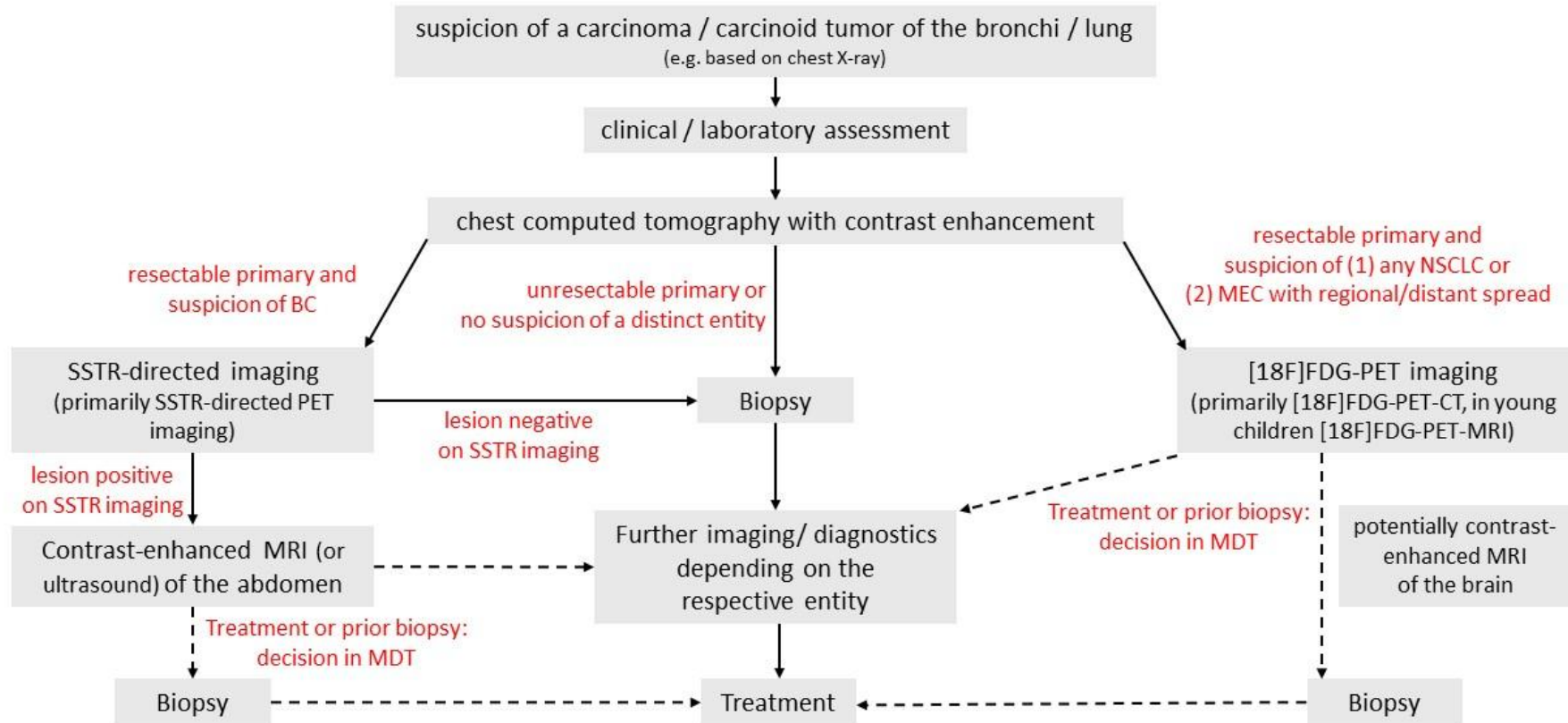
³ M component

- M1 Distant metastasis
 - M1a Tumor with pleural or pericardial nodules or malignant pleural or pericardial effusions, separate tumor nodule(s) in a contralateral lobe
 - M1b Single extrathoracic metastasis in a single organ system
 - M1c Multiple extrathoracic metastases
 - M1c1 Multiple extrathoracic metastases in a single organ system
 - M1c2 Multiple extrathoracic metastases in multiple organ systems

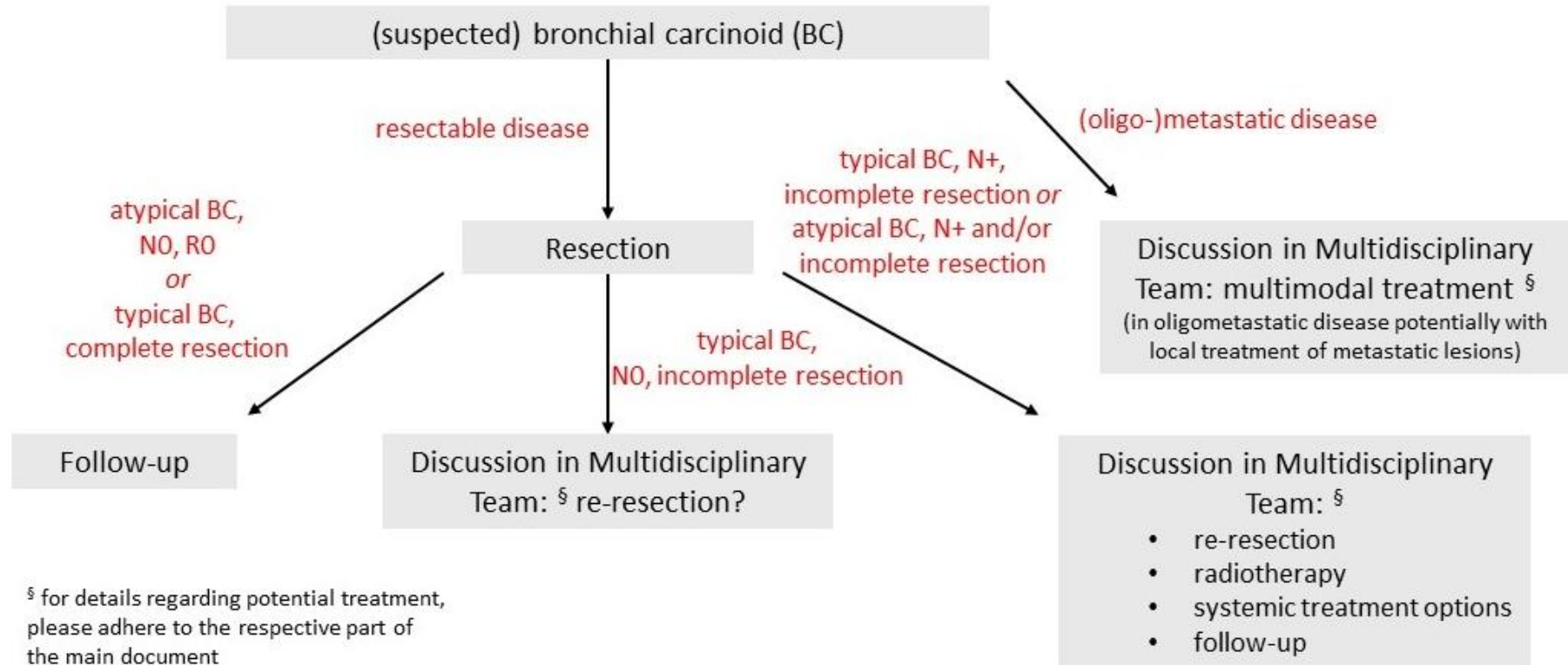
Supplemental Table 3. Follow-up recommendations for non-small cell lung cancer (NSCLC) / Mucoepidermoid carcinoma (MEC) and Bronchial carcinoids (BC) in pediatric patients.

	Non-small cell lung cancer (NSCLC) / Mucoepidermoid carcinoma (MEC)		Bronchial carcinoids (BC)	
	Stage I - III	Stage IV	Completely resected, localized typical BC	Atypical BC, BC with resected metastases/after incomplete resection
History, physical examination	<ul style="list-style-type: none"> every 3 months for 2-3 years after end of treatment, then every 6 months until 5 years after end of treatment, then every 12 months until at least 10 years after end of treatment 	<ul style="list-style-type: none"> every 3 months for 5 years after end of treatment, then every 6-12 months until at least 10 years after end of treatment 	<ul style="list-style-type: none"> every 6 months for the first 2 years, then every 12 months until at least 10 years after end of treatment 	<ul style="list-style-type: none"> every 3 months for the first 2 years, then every 6 months until 5 years after end of treatment, then every 12 months thereafter until at least 10 years after end of treatment
Laboratory workup	depending on the medical treatment received	depending on the medical treatment received	serum chromogranin-A (if pre-operatively positive); further parameters depending on the medical treatment received	serum chromogranin-A; further parameters depending on the medical treatment received
contrast-enhanced chest CT scan	<ul style="list-style-type: none"> every 3 months for 2-3 years after end of treatment, then every 6 months until 5 years after end of treatment 	<ul style="list-style-type: none"> every 3 months for 5 years after end of treatment, then every 6-12 months until at least 10 years after end of treatment 	-	<ul style="list-style-type: none"> at 3, 6, and 12 months in the first year, then every 6 months for a total of at least 2 years, then, chest CT scans and chest X-ray may be performed alternately every year in metastatic and/or atypical BC.
Further imaging	-	Whole-body imaging depending on the localization of metastases/initial imaging (MRI or FDG-PET/CT or FDG-PET/MRI): <ul style="list-style-type: none"> every 3 months for 5 years after end of treatment, then every 6-12 months until at least 10 years after end of treatment 	-	MRI scans (or ultrasound examinations) of the abdomen: <ul style="list-style-type: none"> at 3, 6, and 12 months in the first year, then every 6 months for a total of at least 2 years In atypical BC and/or BC with resected metastases: <ul style="list-style-type: none"> [68Ga]GaDOTA-TATE PET/CT at least once during follow-up (1 year after surgery)
Further diagnostics	<ul style="list-style-type: none"> Ultrasound of the thyroid gland every 2 years after neck irradiation Respiratory function test every 1-2 years after thoracic surgery 		<ul style="list-style-type: none"> Respiratory function test every 1-2 years after thoracic surgery 	

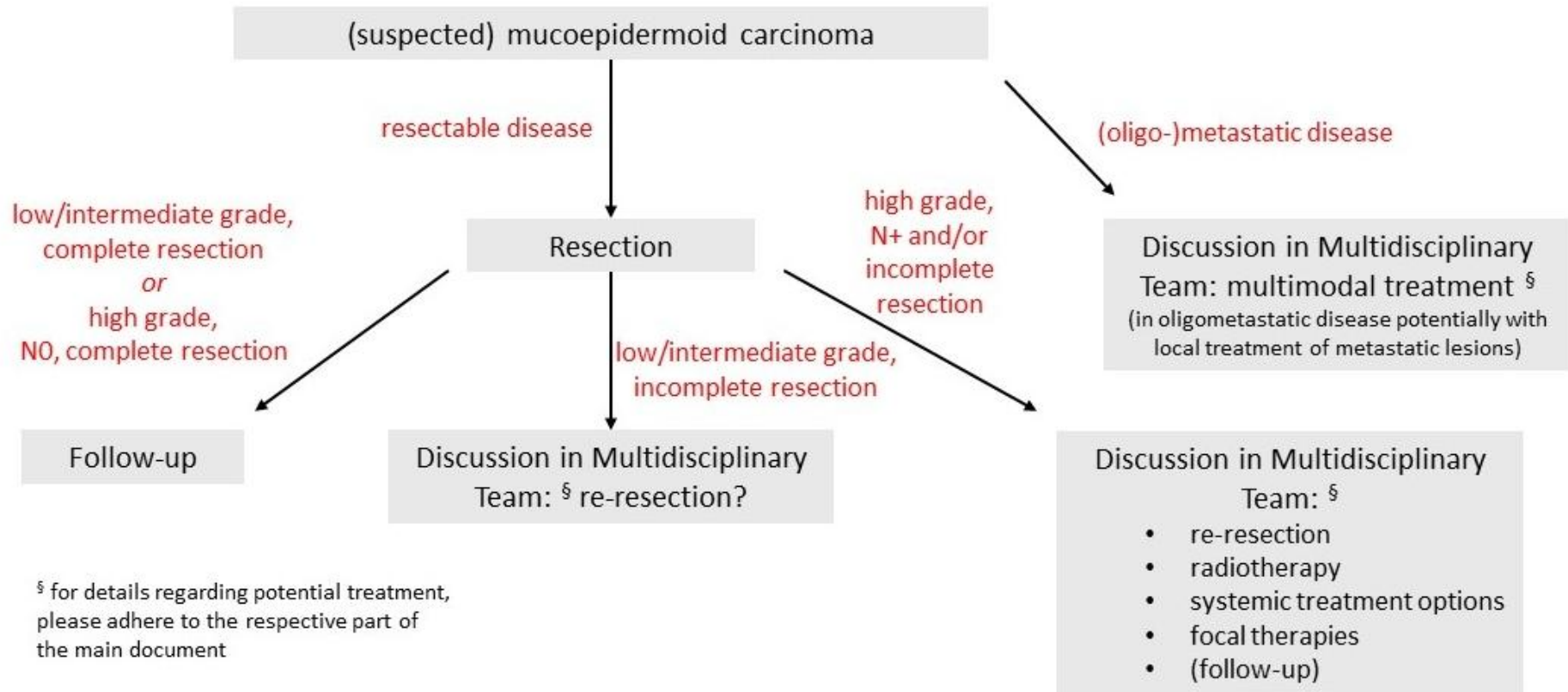
Supplemental Figure 1. Proposed diagnostic approach to pediatric patients with suspicion of a carcinoma / carcinoid tumor of the lung/bronchi.



Supplemental Figure 2. Proposed therapeutic approach to pediatric patients with (suspected) bronchial carcinoid tumors.



Supplemental Figure 3. Proposed therapeutic approach to pediatric patients with (suspected) mucoepidermoid carcinoma of the lung/bronchi.



Supplemental Figure 4. Proposed therapeutic approach to pediatric patients with (suspected) non-small cell lung cancer.

