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ONCOLOGY: RESEARCH ARTICLE

Incidences and characteristics of primary lung malignancies in childhood in Germany: An analysis of population-based data from German cancer registries

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Abstract

Background: Primary lung malignancies are a heterogeneous group of cancers that occur very rarely in childhood. Due to limited knowledge of their epidemiologic and clinical features, these tumors present a challenge to the treating physicians. This study aimed to increase the knowledge about the occurrence of primary lung malignancies in childhood in Germany.

Materials and methods: Pseudonymized data of cases recorded at the German Center for Cancer Registry Data (ZfKD) between 1990 and 2017 were retrieved. Primary lung malignancies were identified using the ICD- and ICD-O classification. Numbers were compared to those reported to the German Childhood Cancer Registry (GCCR). Crude incidence rates were calculated using the ZfKD database.

Results: A total of 168 patients diagnosed with primary lung malignancies in the age below 19 years were identified from the ZfKD. The median age at diagnosis was 13 years. The most common tumor entities were lung carcinoids (n = 49), lung carcinoma (n = 36), and pleuropulmonary blastoma (n = 14). An unexpected accumulation of lung cancer cases was noted in the first year of life without a clearly specified histopathological diagnosis. A substantial discrepancy in the numbers of primary lung malignancies between ZfKD and GCCR was found.

Conclusions: We present population-based data on the occurrence of primary childhood lung malignancies in Germany, which were more frequent than previously anticipated but likely remained underreported. For better understanding and optimal treatment of these entities, cancer registration needs to be improved through mandatory

Abbreviations: CPAM, congenital pulmonary airway malformation; EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; GCCR, German Childhood Cancer Registry; GPOH, German Society for Pediatric Oncology and Hematology; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; IMT, inflammatory myofibroblastic tumors; MEC, mucoepidermoid carcinoma; MET, German Registry for Malignant Endocrine Pediatric Tumors; NSCLC, non-small cell lung cancer; PPB, Pleuropulmonary blastoma; SCLC, Small-cell lung cancer; SEER, Surveillance, Epidemiology, and End Results Registry; STEP, German Registry for Rare Pediatric Tumors; ZfKD, German Center for Cancer Registry Data.

reporting to the GCCR and regular data sharing between GCCR, population-based and clinical cancer registries.

KEYWORDS
epidemiology, German Childhood Cancer Registry, Germany, lung cancer, pediatric oncology, rare tumors

1 | INTRODUCTION

Primary lung malignancies account for less than 0.5% of all childhood cancers and only a few cases are reported annually to the German Childhood Cancer Registry (GCCR), which registers approximately 2200 incident cancer diagnoses in children and adolescents < 18 years of age every year. [1–4] Primary malignant lung tumors comprise only a proportion (15%–20%) of all lung malignancies, compared to the more frequent metastatic lung lesions such as metastases of nephroblastoma or osteosarcoma.[1,5] Primary lung malignancies in childhood are a heterogeneous group that is classified as very rare cancers with a crude annual incidence rate < 2/1,000,000.[6] In contrast, lung cancer is one of the most common solid cancers in adults. The majority of pediatric primary lung malignancies have an epithelial origin which applies to adenocarcinoma, squamous cell carcinoma, and mucoepidermoid carcinoma (MEC), whereas small-cell lung cancer (SCLC) and lung carcinoids are categorized as neuroendocrine tumors. Lung carcinoids, MEC, and adenoid-cystic carcinoma arise endobronchially and were historically grouped as bronchial adenoma.[7] Since 2015, however, these cancers are classified as (Lung Carcinoids belong to carcinoid tumors now, MEC and adenoid-cystic carcinoma belong to salivary gland type tumors).[8] There are also reports of various rare sarcoma entities such as synovial sarcoma and rhabdomyosarcoma, malignant peripheral nerve sheath tumors, and lymphoma with primary localization in the lung.[9–16] Inflammatory myofibroblastic tumors (IMT) assemble from inflammatory cells, collagen, and myofibroblastic mesenchymal spindle cells.[17,18] Due to their potential for local invasion and recurrence, the IMT were reclassified as intermediary lesions of borderline malignancy in 2015.[8,19] Finally, pleuropulmonary blastoma is a characteristic primary lung tumor of infancy and childhood that may mimic embryonal lung structures and develops in the context of germline *DICER1* mutation.[20]

As with most childhood cancers, the etiology of primary lung malignancies in childhood remains poorly understood. Besides having an association with cancer predisposition syndromes like Li–Fraumeni syndrome, some primary lung malignancies are linked to structural alterations like congenital pulmonary airway malformations (CPAM) or recurrent respiratory papillomatosis.[21–24] Lung tumors occur rarely as second malignant neoplasms, usually after the radiation therapy to the chest, e.g. as a treatment for Hodgkin's disease. [25,26] Secondary lung malignancies, however, usually do not appear until adulthood.[25]

The rare occurrence and various underlying histologic entities of primary lung malignancies in children pose a serious challenge for the treating physicians. The present study aimed to improve our understanding of the epidemiology of these tumors by estimating more accurate incidence rates which are of considerable importance for future studies on diagnostics and treatment modalities.

2 | MATERIALS AND METHODS

We obtained data from the German Center for Cancer Registry Data (ZfKD), the national cancer registry that receives data from the population-based cancer registries of all German federal states as required by the Federal Cancer Registry Data Act.[27] All patients recorded by the ZfKD who met the following inclusion criteria were involved in the analysis: diagnosis of a malignant disease with the following codes of the International Classification of Diseases (ICD) C34-C34.9, D02.2, first diagnosis in the age below 19 years and between 1990 and 2017. Importantly, due to structural changes in registration requirements, not all federal registries reported to the ZfKD for the entire timespan of cancer patients. The ZfKD only received data from all federal registries from 2009 to 2015. An overview of the respective reportings by year and registry including the reported follow-up is provided inSupporting Information. IMT was not included in the ZfKD recordings.

Pseudonymized data were gathered from the ZfKD for patient-related data (sex, month and year of birth, federal state, month and year of death, cause of death according to ICD) and tumor-related data (age at diagnosis, cancer site, and histology as per the International Classification of Diseases for Oncology (ICD-O), status per TNM-Classification of Malignant Tumors (TNM), grading). One limitation of the present study is that data on TNM staging was missing in about 50% of cases in the ZfKD records.

We calculated crude incidence rates for the patients under 19 years of age as the number of cases per person-years calculated as the average population count between 2009 and 2015 as reports from all state registries was obtained from the ZfKD. Childhood population data were obtained from the Federal Statistical Office of Germany.[28]

We also obtained data from the German Childhood Cancer Registry (GCCR), the nationwide population-based childhood cancer registry that monitors incident cases of all malignancies as well as non-malignant central nervous system tumors diagnosed in 0- to 17-year-olds with the place of residence in Germany and that is the primary source for analyses and reports on childhood cancer in Germany.[4,29] The GCCR receives daily reporting from all pediatric hematology-oncology units in Germany (subject to the patients' or custodians' consent). Regular data exchange with clinical therapy studies and

TABLE 1 Patient characteristics and clinical features of primary childhood lung malignancies registered at the German Center for Cancer Registry Data 1990–2017[a] and at the German Childhood Cancer Registry 1980–2019[b]

	German Center for Cancer Registry Data (ZfKD) 1990–2017 ($n = 168$)			German Childhood Cancer Registry (GCCR)1980 – 2019 ($n = 98$)		
Characteristics	**Count**	**Proportion**	**Relative frequency after exclusion of unspecified malignancies**	**Count**	**Proportion**	**Relative frequency after exclusion of inflammatory myofibroblastic tumors**
Sex						
Male	99	58.9%		52	53.1%	
Female	69	41.1%		46	46.9%	
Age at diagnosis						
< 10	71	42.3%		42	42.9%	
≥ 10	97	57.7%		56	57.1%	
Histology						
Adenocarcinoma	18	10.7%	15.5%	2	2.0%	2.5%
Squamous cell carcinoma	6	3.6%	5.2%	4	4.1%	4.9%
Adenosquamous carcinoma	1	0.6%	0.9%	0	0%	0%
Small-cell lung cancer	5	3.0%	4.3%	0	0%	0%
Mucoepidermoid carcinoma	6	3.6%	5.2%	12	12.2%	14.8%
Lung carcinoid	49	29.2%	42.2%	25	25.5%	30.9%
Pleuropulmonary blastoma	14	8.3%	12.1%	20	20.4%	24.7%
Rhabdomyosarcoma	4	2.4%	3.4%	4	4.1%	4.9%
Other sarcomas	7	4.2%	6.1%	9	9.2%	11.1%
Other specified malignancies	6	3.6%	5.2%	5	5.1%	6.2%
Unspecified malignancies	52	31.0%	–	–	–	–
Inflammatory myofibroblastic tumor[c]	–	–	–	17	17.3%	–

[a]0–18 years, no inflammatory myofibroblastic tumors registered with the ZfKD.
[b]0–14 years before 2009, 0–17 years since 2009, no unspecified malignancies reported to the GCCR.
[c]No inflammatory myofibroblastic tumors were reported to the ZfKD, inflammatory myofibroblastic tumors were reported incompletely to the GCCR.

other clinical databases of pediatric oncological patients, as well as a close and well-established collaboration with the German Society for Pediatric Oncology and Hematology (GPOH) guarantee that almost all childhood cancer cases are recorded. Before 2009, however, only patients aged < 15 years were registered by the GCCR. All patients prospectively recorded by the GCCR who met the following inclusion criteria were included in the analysis: diagnosis of a malignant disease with the following ICD codes: C34 - C34.9, D02.2, D38.1 and diagnosis between 1980 and 2019. Pseudonymized data were obtained from the registry for both, patient-related data (sex, month and year of birth, federal state) and tumor-related data (month and year of diagnosis, age at diagnosis, cancer site, and histology as per ICD-O).

As this is a retrospective analysis of cancer registry data, the data could not be verified with primary source data.

3 | RESULTS

A total of 168 cases of primary lung malignancies had been reported to the ZfKD for the diagnostic period 1990 to 2017. Characteristics of these patients are presented in Table 1. The median age at diagnosis was 13 years (mean: 10.1 years) with male children and adolescents were slightly more prevalent in the sex and age distributions. The most common subtype of specified lung malignancies was lung carcinoids ($n = 49$), followed by lung carcinoma ($n = 36$) and pleuropulmonary blastoma ($n = 14$). A total of 52 cases were recorded with a nonspecific ICD-O code as malignant neoplasms without further specification.

Lung carcinoids were predominantly found in adolescents with a median age at diagnosis of 16 years (range 0–18 years) and a slight male predominance (55%). Lymph node metastases were reported in only 16.7% of cases with no reports of distant metastases. Only one patient with lung carcinoid was reported as deceased during the covered follow-up period.

The group of lung carcinoma was subdivided into non-small-cell lung cancer (NSCLC), SCLC, and MEC. NSCLC and MEC occurred mainly in adolescents, with a median age of 16 years and 17 years at diagnosis, respectively (NSCLC: range 0–18 years, MEC: range 6–18 years). Notably, three of five patients with SCLC were diagnosed within the first year of life, whereas the other two presented in adolescence. In patients with MEC and SCLC, a stronger male predominance was detected with ≥80% incidence. NSCLC and SCLC

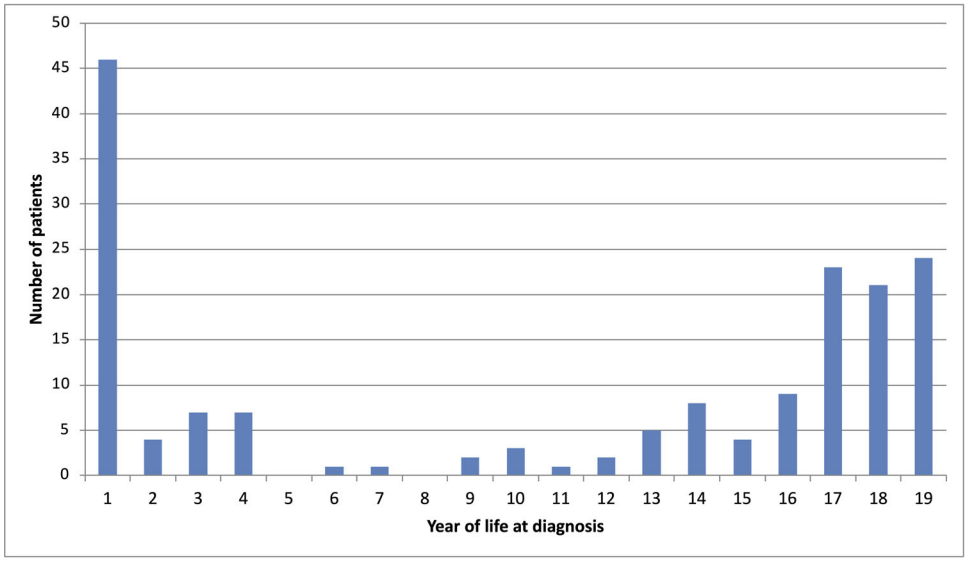

FIGURE 1 Age distribution (in years of life, age < 19 years) at diagnosis of primary lung malignancies as recorded in the German Center for Cancer Registry Data 1990—2017

were frequently detected at an advanced stage. Lymph node and distant metastases were found in the majority of these patients, in sharp contrast to those with MEC. For 33% of patients with NSCLC and SCLC, death was reported to the ZfKD while none of the patients with MEC was reported as deceased.

Patients with pleuropulmonary blastoma (PPB) were mainly diagnosed in early childhood with a median age at diagnosis of 2 years (range 0–13 years). Reports on the death of two patients with PPB were submitted to the ZfKD.

In general, there were two peaks of registration: in the first year of life and in late adolescence, as shown in Figure 1. Death was recorded for 65 of 168 patients at the last follow-up. Of 46 patients diagnosed in the first year of life, 31 died within that first year. For the other patients, the mean age at death was 14.7 years with an average timespan from diagnosis to death was 0.9 years.

In 50 patients, the months and years of diagnosis were identical to the months and years of death, indicating that the diagnosis was often made at an advanced stage of disease or at death.

In comparison, 98 patients with primary lung malignancies were reported to the GCCR from 1980 to 2019. However, patients aged 15–17 years have only been recorded since 2009. Thus, the majority of GCCR cases (58.2%) were reported during the period 2009 to 2019. The characteristics of patients recorded by the GCCR are presented in Table 1. Similar to the ZfKD data, the median age at diagnosis was 11 years (mean: 9.7 years) with male children and adolescents slightly more prevalent in the sex and age distributions. In contrast to the ZfKD, the GCCR data also include the reported cases of IMT. The registration of lung carcinoids and NSCLC and/or SCLC increased substantially after 2009, as shown in Table 2. However, the frequency of NSCLC and SCLC in the GCCR remained lower than in the corresponding data from the ZfKD.

In the period between 2009 and 2015, the reporting conditions of the ZfKD and the GCCR were aligned (all federal states, < 18 years of age at diagnosis). Over this timespan, the ZfKD recorded 77 cases, whereas only 30 cases were registered in the GCCR as displayed in Table 3. Since the ZfKD data did not include IMT, only 22 cases of comparable primary lung malignancies were reported to the GCCR. Moreover, 49 of the 77 cases in the ZfKD had specific ICD-O-codes.

Based on the cases recorded by the ZfKD from 2009 to 2015, crude incidence rates were determined for primary lung malignancies in Germany, as displayed in Table 4. The crude incidence rate of these entities was 0.83 per million in 2009–2015.

TABLE 2 Registration of lung carcinoids and NSCLC/SCLC in the reported data from the German Childhood Cancer Registry before and after inclusion of patients aged 15–17 years in 2009

Entity	Count	
Lung carcinoid		
1980–2008	6	
2009–2019	19	thereof 13 patients aged 15–17 years
NSCLC/SCLC		
1980–2008	1	
2009–2019	5	thereof 3 patients aged 15–17 years

Abbreviations: NSCLC: non-small-cell lung cancer, SCLC: small-cell lung cancer.

4 | DISCUSSION

Previous literature attributed 0.2%–0.3% of all childhood cancers to primary lung malignancies, corresponding to an annual crude incidence rate of 0.49 per million.[2,3,30] Our analysis of the ZfkD data revealed a total crude incidence rate of 0.83 per million, corresponding to approximately 0.5% of all childhood cancers in Germany which probably still reflects some underreporting.

TABLE 3 Comparison of primary childhood lung malignancies in patients aged 0–17 years recorded in the German Center for Cancer Registry Data and the German Childhood Cancer Registry 2009–2015

Entity	Count German Center for Cancer Registry Data	Count German Childhood Cancer Registry
Adenocarcinoma	7	1
Squamous cell carcinoma	2	1
Adenosquamous carcinoma	0	0
Small-cell lung cancer	3	0
Mucoepidermoid carcinoma	4	3
Lung carcinoid	17	11
Pleuropulmonary blastoma	8	4
Rhabdomyosarcoma	1	0
Other sarcomas	3	2
Other specified malignancies	4	1
Inflammatory myofibroblastic tumor	Not included	7
Unspecified malignancies	28	0

TABLE 4 Crude incidence rates of primary lung malignancies in patients aged 0–17 years as recorded in the German Center for Cancer Registry Data 2009–2015

Entity	Count	Crude incidence rate per million
Adenocarcinoma	7	0.076
Squamous cell carcinoma	2	0.022
Adenosquamous carcinoma	0	–
Small-cell lung cancer	3	0.032
Mucoepidermoid carcinoma	4	0.043
Lung carcinoid	17	0.184
Pleuropulmonary blastoma	8	0.086
Rhabdomyosarcoma	1	0.011
Other sarcoma	3	0.032
Other specified malignancies	4	0.043
Inflammatory myofibroblastic tumor	Not included	Not included
Unspecified malignancies	28	0.302
Total	77	0.832

The specifications for pediatric oncology centers within the comprehensive cancer centers in Germany require treatment of all children and adolescents with cancer in pediatric oncology departments, at least in addition to therapy in adult oncology units. Thus, all children and adolescents with cancer in Germany should be reported to the GCCR (subject to the patients' or custodians' consent). Our data indicate that these requirements are not fully met for rare childhood tumors and that consequently there is a registration gap in the GCCR regarding these rare cancer entities. Part of the difference in registration between ZfKD and GCCR may be attributed to higher registration completeness of the ZfKD because cancer cases are reported to the federal cancer registries by treating physicians as well as pathologists regardless of the treating department and age. As many epithelial lung malignancies occur predominantly in adolescence, a substantial proportion of these patients may have been treated in adult oncological treatment units and was not reported to the GCCR. This hypothesis is supported by our comparison of registrations in the ZfKD and the GCCR between 2009 and 2015. While patient characteristics of specific entities are similar in both registries, lung carcinomas appear underreported in the GCCR, which currently receives only notifications from pediatric hematology-oncology units. Then again, it seems likely that younger children remained underreported in the state registries as pediatric oncologists were originally accustomed to reporting to the GCCR only.

However, a relevant proportion of primary lung malignancies recorded by the ZfKD did not have specific ICD-O morphology codes. While some of these patients appear to have been diagnosed at an advanced stage of disease based on imaging and clinical condition and

TABLE 5 Entity distribution of specified primary lung malignancies in the German Center for Cancer Registry Data, SEER and literature without consideration of inflammatory myofibroblastic tumors

Entity	Relative frequency German Center for Cancer Registry Data	Relative frequency SEER[30]	Range of relative frequencies in literature[7,18,30,32]
Lung carcinoid	42.2%	51.6%	30%–63%
Pleuropulmonary blastoma	12.1%	9%	9%–30%
NSCLC/SCLC	25.9%	15.5%	15%–20%
Mucoepidermoid carcinoma	5.2%	9%	9%–22%
Rhabdomyosarcoma	3.4%	Not specified	5%
Other specified malignancies	11.3%	14.9% including rhabdomyosarcoma	0%–15%

Note: Specifications of literature: [18] age < 18 years,[32] age < 19 years, without consideration of pleuropulmonary blastoma,[7,30] age < 20 years.
Abbreviations: SEER: Surveillance, Epidemiology, and End Results Registry.

may have undergone palliative treatment without any intervention, many infants were registered with topographic ICD codes for lung malignancies without specific morphology codes or TNM status as well. Of the 32 cases with an age at diagnosis of less than 1 year and nonspecific ICD-O-code 8000/3 (malignant neoplasm), only one patient was reported with the TNM status. Thirty of these patients died within one month of diagnosis or were diagnosed with lung malignancies at the time of death. This phenomenon was unexpected and raises some questions. Rapid deaths of infants associated with suspected pulmonary malignancies are not common in our clinical experience. Although type-II and type-III PPBs are associated with relevant lethality in infancy and the ZfKD presumably has not received updates by referral pathologists, it is unlikely that many of these cases are PPB based on the current knowledge on the frequency of PPB.[31] As 18 of these cases were reported by a single state registry, we suspect that some of these registrations may contain inaccurate information and may have been reported with incorrect topographic ICD codes. Unfortunately, we cannot confirm this suspicion because reverse fact-checking and primary source data validation was not possible due to the General Data Protection Regulation. Therefore, the total crude incidence rate must be considered with caution in contrast to the crude incidence rates of the specific entities.

The median age at diagnosis of primary lung malignancies in childhood in our analysis was comparable with previously reported ranges from 9 to 16 years.[2,30,32] We found a slight male predominance consistent with the underlying general population. Previous publications reported an approximately equal sex distribution.[30,32,33]

Our evaluation of ZfKD data provides a comprehensive analysis of the distribution of the different lung malignancy entities, although a certain degree of unspecificity regarding coding cannot be excluded. There are several reports on this aspect with markedly varying results depending on the underlying data sources, as shown in Table 5. As primary lung malignancies are very rare tumors, analyses with small patient samples can quickly lead to biased perceptions, which might contribute to these differences. The analysis of the American Surveillance, Epidemiology, and End Results Registry (SEER) by Neville et al. based on 160 patients and comparable inclusion criteria used by us identified similar proportions of the different subtypes, supporting our findings.[30]

Lung carcinoids are mostly endobronchial tumors with low malignant potential, more common in childhood than in adulthood.[7,34,35] Our data are consistent with the more frequent occurrence of these cancers in adolescence.[36,37] In our patient sample, only six cases with lymph node metastases and no cases with distant metastases were recorded. Only 1 out of 49 patients was reported as deceased to the ZfKD, confirming previous reports of survival probabilities between 90% and 95% due to excellent surgical therapeutic approaches.[30,32,38]

The subgroup of bronchogenic carcinoma includes adenocarcinoma, squamous cell carcinoma, and SCLC and has a most aggressive and metastatic behavior linked with high lethality.[39] For adenocarcinoma, the median age at diagnosis in our analysis was 17 years, which is consistent with that in previous findings.[40] Lymph node metastases were reported in 60% of cases, and 43% had a distant metastatic spread, resulting in advanced disease stages at diagnosis. This too is consistent with previous publications.[40] The outcome for adenocarcinoma is very poor with an overall survival probability of 26%.[30,32]

Six cases of squamous cell carcinoma of the lung were recorded at the ZfKD with a median age at diagnosis of 8 years. Lymph node and distant metastatic lesions were reported in two cases each, displaying the known aggressive tumor characteristics.[41] As with adenocarcinoma of the lung, treatment approaches for children and adolescents are based on adult therapy guidelines. The reported 5-year overall survival rate of pediatric patients with these tumors is 28%.[32] Although accounting for 15% of all lung carcinomas in adults, SCLC is extremely rare in childhood according to our literature review.[42] Five patients with SCLC were recorded by the ZfKD. Of these, three patients were diagnosed with advanced disease stages within the first three months of life, whereas the SEER analysis found this entity exclusively in patients aged 15 years or older.[30] Lymph node metastases were found in all three cases and distant metastases in two cases. The etiology of these tumors remains unclear. Therefore, it must again be considered critically whether these tumors might have been falsely attributed to SCLC and could potentially rather have presented as PPB. As an alternative hypothetical explanation, there are reports of

transplacental and vaginal transmission of carcinomas from mothers with cancer to infants who develop SCLC and adenocarcinomas of the lung.[43–45]

MEC is an endobronchial malignancy arising from submucosal bronchial glands with a mixture of squamous cells and mucus-secreting cells.[46] It is histologically comparable to the more common salivary gland MEC.[47,48] As in our patient sample, MEC mostly occurs in adolescents and young adults.[49] These tumors are mostly characterized by MECT1/MAML2 fusion transcripts.[50] No lymph nodes or distant metastatic lesions were found in our data. This finding reinforces the impression that there are biological differences between MEC in childhood and MEC in adulthood.[50,51] While adult MEC has lymph node involvement in up to 50% of cases and distant metastases in up to 15% of cases, advanced disease stage with metastases in childhood is rare.[50] This is reflected in the overall survival rates. Childhood MEC's 5-year overall survival is 100% after complete resection, whereas the 1-year overall survival probabilities are 20%–80% for adult MEC, depending on the tumor grading.[30,32,52] These data are consistent with the patients registered with the ZfKD, none of whom have been reported deceased.

PPBs are of mesenchymal origin with primitive embryonal-like blastema and stroma and are classified into three distinct types depending on the mixture of cystic and solid components.[1,53] While type I-PPB has a higher cystic component and a younger mean age of 8 months at diagnosis that results in a more favorable outcome (5-year overall survival, 86%–91%), type-II-PPB and type-III-PPB occur in older children (35 months and 41 months, respectively), have more solid tumor components and are associated with a worse outcome despite the addition of chemotherapy to surgical treatment options (5-year overall survival 53–71%).[20,54] In our analysis, mean age at diagnosis of 3.1 years was observed for these patients, indicating a higher proportion of type-II- and type-III-PPB. Most children with PPB have a heterozygous DICER1 germline variant, but this mutation has no prognostic impact.[20,55]

Since the ZfKD receives epidemiological data from the regional state registries, the data collected on treatment modalities are only superficial. This shows the clear necessity for a consistent registration of these cancers in the GCCR and in the corresponding registries of the GPOH, e.g., the German Registry for Rare Pediatric Tumors (STEP) and the German Registry for Malignant Endocrine Pediatric Tumors (MET). Only continuous recording and evaluation of diagnostic and therapeutic modalities can successively improve the treatment of primary lung malignancies.

5 | CONCLUSIONS

Our analysis provides a more accurate picture of the incidence of primary lung malignancies in childhood in Germany than previous assessments. Their occurrence is more frequent than was previously estimated. A substantial discrepancy between the registration frequency of these cancers in the GCCR and the ZfKD, particularly in adolescent cases, demonstrates the need for mandatory nationwide reporting of all childhood. An optimized coverage in the GCCR as well as in the STEP/MET registry is a prerequisite for a better understanding of these entities and further research, including tumor genomic profiling. This may also help to clarify the unexpected accumulation of lung cancer cases in the first year of life without a clearly assignable cause. While adult oncology therapy units are generally more familiar with lung cancer treatment, the occurrence of childhood carcinomas is more often linked with tumor predisposition syndromes and specific mutations.[56] In addition, long-term therapy-associated morbidity has a stronger impact on the treatment of pediatric patients than in adults.[57] Therefore, an interdisciplinary network of childhood and adult cancer experts like the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) is needed to ensure optimal treatment of these tumors in childhood according to the latest clinical experience and research findings. Furthermore, evidence-based pediatric guidelines for the diagnosis and treatment of primary lung malignancies must be developed in future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Michael Abele, Sarah Voggel, Claudia Bremensdorfer, Claudia Spix, Friederike Erdmann, Michaela Kuhlen, Antje Redlich and Ines B. Brecht. The first draft of the manuscript was written by Michael Abele, Sarah Voggel, and Ines B. Brecht and all authors commented on previous versions of the manuscript. All authors contributed to the data interpretation, critically reviewed the manuscript for important intellectual content, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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