Journal of Pediatric Surgery 50 (2015) 1004–1008

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Primary malignant pulmonary tumors in children: a review of the national cancer data base

Yesenia Rojas [a], Yan X. Shi [a], Wei Zhang [b], Elizabeth A. Beierle [c], John J. Doski [d], Melanie Goldfarb [e], Adam B. Goldin [f], Kenneth W. Gow [f], Monica Langer [g], Sanjeev A. Vasudevan [a], Jed G. Nuchtern [a,*]

[a] Michael E. DeBakey Department of Surgery, Baylor College of Medicine, and Department of Surgery, Texas Children's Hospital, Houston, TX
[b] Outcomes and Impact Service, Department of Surgery, Texas Children's Hospital, Houston, TX
[c] Department of Surgery, University of Alabama, Birmingham, AL
[d] Department of Surgery, Methodist Children's Hospital of South Texas, University of Texas Health Science Center – San Antonio, San Antonio, TX
[e] Department of Surgery, John Wayne Cancer Institute/Providence St. Johns Medical Center, Santa Monica, CA
[f] Department of Surgery, Seattle Children's Hospital, University of Washington, Seattle, WA
[g] Department of Surgery, Maine Children's Cancer Program, Tufts University, Portland, ME

ARTICLE INFO

Article history:
Received 26 February 2015
Accepted 10 March 2015

Key words:
Primary lung cancer
Pediatric
National Cancer Database (NCDB)
Population-based study

ABSTRACT

Background: The purpose is to delineate the clinical and pathological characteristics of rare primary malignant pulmonary tumors in children.
Methods: Utilizing the National Cancer Data Base (NCDB), we analyzed all children (≤18 years) with a primary malignant pulmonary tumor from 1998 to 2011 to identify factors associated with better survival.
Results: Of 211 children identified, the most common histology was carcinoid tumor (n = 133, 63%) followed by mucoepidermoid carcinoma (MEC) (n = 37, 18%), squamous cell carcinoma (SCC) (n = 19, 9%), adenocarcinoma (n = 16, 8%), bronchoalveolar carcinoma (BAC) (n = 4, 2%), and small cell carcinoma (SCLC) (n = 2, <1%). Factors that significantly affected survival include histology, race, tumor size, lymph node status, and extent of surgery. Patients with MEC and carcinoid tumors had a better overall survival compared to patients with other histologies ($p < 0.0001$). The 5-year overall survival for MEC and carcinoid tumors was 100% and 95% (95% CI 87–98), respectively, versus 50% (95%CI 1–91) for BAC, 28% (95%CI 9–52) for SCC, and 26% (95%CI 5–55) for adenocarcinoma.
Conclusion: The majority of pediatric patients with a primary malignant pulmonary tumor present with carcinoid tumor or MEC and have an excellent prognosis. Lung cancers which are common in adults, but rare in children, have a worse prognosis.

The diagnosis of a primary malignant lung tumor in children is difficult to make given the non-specificity of symptoms and rarity of the disease. The overall incidence of primary malignant tumors in the pediatric population is estimated to be 0.049 per 100,000 persons [1]. Metastatic and benign tumors are far more common than primary malignancies where the reported ratio of primary malignant to benign to metastatic is 1:5:60 [2]. Common metastatic tumors include Wilms tumors, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma [3,4]. Previously described benign lesions include inflammatory myofibroblastic tumors, hamartomas, and chondromas [2,4].

Primary malignant lung tumors of epithelial origin in pediatric patients are the same as those reported in the adult population but differ in incidence and clinical behavior [3]. These include adenocarcinoma, bronchoalveolar carcinoma (BAC), squamous cell carcinoma (SCC), small cell carcinoma (SCLC), mucoepidermoid (MEC), and carcinoid tumors [3]. Currently the pediatric literature primarily consists of case reports and case series [3,5–7]. In the most recent institutional experience, Yu *et al.* reported on 40 children with both benign and malignant lung tumors in a span of 90 years, highlighting the rarity of this disease [2]. Only one population-based study has been published using the Surveillance, Epidemiology, and End Results (SEER) database and includes 160 patients from 1973 to 2004 [1]. The purpose of this study was to delineate the clinical and pathological characteristics of rare primary malignant pulmonary tumors in children reported in the National Cancer Data Base.

1. Material and methods

1.1. Source of data and patient selection

The authors were granted access to the National Cancer Data Base (NCDB), a joint program of the Commission on Cancer (CoC) of the American College of Surgeons (ACoS) and the American Cancer Society.

* Corresponding author at: Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Texas Children's Hospital, Baylor College of Medicine. Tel.: +1 832 822 3135; fax: +1 832 825 3141.
E-mail address: nuchtern@bcm.edu (J.G. Nuchtern).

http://dx.doi.org/10.1016/j.jpedsurg.2015.03.032
0022-3468/

It is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that captures 70% of all newly diagnosed malignancies in the United States [8]. Patients <18 years of age with a primary malignant pulmonary tumor diagnosed from 1998 to 2011 were included in this study. Pulmonary tumor histologies of epithelial origin specific to the lung and bronchus were identified using the International Classification of Disease for Oncology, 3rd edition. (804X – small cell carcinoma, 807X – squamous cell carcinoma, 814X – adenocarcinoma, 824X – carcinoid tumor, malignant, 825X – bronchoalveolar carcinoma, and 843X – mucoepidermoid carcinoma) specific to the lung and bronchus. Only patients with a single primary malignancy were in this study. Patients in each histology group were compared for differences in age, gender, race, tumor size, lymph node involvement, treatment specifics, length of follow-up, and 5-year overall survival (OS).

1.2. Statistical analysis

Statistical significance was determined by the Fisher's exact test for categorical variables and by the Wilcoxon rank test for continuous variables. Survival curves were constructed using the Kaplan-Meier method and strata were compared with the log-rank test. Associations between the continuous variables and survival were investigated univariately using the Cox proportional hazard regression. Multivariate analyses were not performed due to the small number patients in some categories. Statistical significance was set at $p \leq 0.05$. Analyses were conducted using SAS 9.3 for Windows (SAS Institute, Cary, NC).

1.3. Ethics and policy

Data reported to the NCDB are retrospective and do not contain patient or physician identifiers. The Participant Use File (PUF), which is distributed from the NCDB to investigators, is a deidentified data file per the regulatory and privacy requirements of the Health Insurance Portability and Accountability Act of 1996 [9].

2. Results

2.1. Demographics, clinical characteristics, and treatment

A total of 211 cases of children ≤18 years of age with a primary malignant pulmonary tumor of epithelial origin were reported to the NCDB from 1998 to 2011. This is an average of 16 cases per year in the United States. The clinical and demographic characteristics are summarized in Table 1. The mean age of diagnosis was 13 years (range 8–17 years). The majority of children were white (77%) with a fairly equal gender distribution (males = 55%) and a minority of patients had a co-morbid disease.

The most common histology was carcinoid tumor (n = 133, 63%), followed by MEC (n = 37, 18%), SCC (n = 19, 9%), adenocarcinoma (n = 16, 8%), BAC (n = 4, 2%), and SCLC (n = 2, <1%). The majority of the patients (n = 173, 82%) underwent known surgical resection of their tumor with regional lymphadenectomy (n = 132, 63%). A minority of the patients received chemotherapy and radiation therapy (14% and 9%, respectively).

Table 2 summarizes tumor characteristics and treatment by histology. The majority of patients with carcinoid tumor and MEC presented with small tumors (≤5 cm), had a local tumor resection or lobectomy, no adjuvant therapy, and achieved a complete R0 resection (>80%). For children with SCC and adenocarcinoma, an equal number of patients presented with tumors ≤5 cm and >5 cm and the majority had involved regional lymph nodes. Most of these patients received chemotherapy, some were treated with radiation, and more than half did not receive surgery as part of their primary treatment. Of the few children that presented with BAC and SCLC, 50% received surgery as part of their initial treatment. All patients with SCLC were treated with radiation and chemotherapy.

Table 1
Demographics, clinical characteristics, and treatment (N = 211).*As defined by Charlston/Deyo Score ≥1.

	N	%
Gender		
Male	115	55
Female	96	45
Race		
White	163	77
Black	32	15
Other	16	8
Co-morbidities*	17	8
Histology		
Carcinoid tumor	133	63
Mucoepidermoid (MEC)	37	18
Squamous cell carcinoma (SCC)	19	9
Adenocarcinoma	16	8
Bronchoalveolar carcinoma (BAC)	4	2
Small cell carcinoma (SCLC)	2	<1
Surgery at primary site		
Yes	173	82
No	34	16
Unknown	4	2
Regional lymphadenectomy		
Yes	132	63
No	51	24
Unknown	28	13
Chemotherapy		
Yes	31	14
No	175	83
Unknown	5	3
Radiation therapy		
Yes	18	9
No	190	90
Unknown	3	1

2.2. Survival analysis

On univariate analyses, factors that significantly affected OS include tumor histology, race, tumor size, lymphadenectomy, lymph node status, and the extent of surgery at the primary site (Table 3). Patients with MEC and carcinoid tumor had a significantly better OS compared to patients with other histologies (Fig. 1). The 5- year OS for MEC and carcinoid tumors is 100% and 95% (95%CI 87–98), respectively, versus, 50% (95%CI 1–91) for BAC, 28% (95%CI 9–52) for SCC, and 26% (95%CI 5–55) for adenocarcinoma. Both patients with SCLC were deceased at 5 years after diagnosis. Black patients and those with tumor size >5 cm had inferior OS when compared to patients of white or other race and tumor size ≤5 cm. The OS for patients who did not have surgery was only 36% (95%CI 17–56). Additionally, patients who had lymphadenectomy as part of their surgery and had negative regional lymph nodes had a superior OS than those who did not.

3. Discussion

Primary malignant lung tumors are rare in children and account for <2% of all pediatric malignancies making diagnosis and evidence based treatment decisions difficult [4,6]. Given the low incidence, it is difficult to study treatment and outcomes of these tumors at an institutional level. To our knowledge, the current study represents the largest population-based study to date of primary malignant pulmonary tumors in children.

Carcinoid tumors are generally a more favorable histology in the spectrum of neuroendocrine tumors [10,11]. The lung is the second most common organ of origin (24%), following small bowel (26%). In the adult population, pulmonary carcinoid tumors account for only 2% of all primary lung cancer [11]. However, in children, carcinoid tumors