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Primary Pediatric Non-Hodgkin Lymphomas of the Gastrointestinal Tract: A Population-based Analysis

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Abstract. *Background/Aim: The aim of this study was to present the clinical characteristics, natural history and survival outcomes of primary gastrointestinal non-Hodgkin lymphomas (PGINHL) in the pediatric population. Patients and Methods: Surveillance, Epidemiology, and End Results (SEER) database was queried for patients aged 0 to 19 years with PGINHL between 1973 and 2014. Results: A total of 452 cases were identified [mean age 11.0 (±5.1)] years, whites 84.1%, males (76.5%). The majority of tumors were noted in the small bowel (SB) (47.6%), followed by large bowel (LB) (28.5%) and the stomach (10.0%). Overall, the most common histological subtype was Burkitt lymphoma (51.8%), followed by diffuse large B-cell lymphoma (DLBCL) (26.1%). Mean overall survival (OS) of the entire cohort was 33,33 years with a 5-yr, 10-yr and 30-yr survival rate of 86%, 86% and 79%, respectively. Large bowel tumors had the best long-term survival rates whereas; gastric tumors had the worst with 30-yr survival rate 84% and 74%, respectively. Overall, 328 (72.6%) patients received surgery. No significant survival difference was noted between patients who underwent surgery and those who did not. Conclusion: This study presents the largest dataset of pediatric PGINHL and describes the clinical features and outcomes of these patients in addition to summarizing the literature.*

Primary gastrointestinal non-Hodgkin lymphomas (PGINHL) are a heterogeneous group of rare tumors, accounting for approximately 30-40% of all extra-nodal non-Hodgkin lymphomas (1). These tumors are comprised of many different histological subtypes with varying disease course, treatment regimens and outcomes (2). Treatment modalities include surgery, radiotherapy, immunotherapy, antibiotics, or a combination of these therapies depending on histological subtype, tumor site and disease presentation (3, 4). Data on natural history and outcomes of PGINHL is limited and one year and 5-yr overall survival (OS) of 65.6% and 35.6%, respectively, has been reported, with no improvement in survival with surgical resection (5, 6). Our current knowledge regarding pediatric PGINHL is limited to case reports and small case series (7-11). Therefore, to better understand the clinicodemographic features and outcomes of these tumors in the pediatric population, we utilized a population-based database to analyze a higher number of patients.

In this study, we evaluated the clinical characteristics, treatment and survival outcomes of pediatric patients with PGINHL utilizing the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database. In addition, we aimed to review previously reported data of PGINHL and investigate any difference in the pediatric data, compared to PGINHL in general.

Patients and Methods

Study population. National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database was utilized for data mining. We extracted all gastrointestinal malignancies in the pediatric population using the age variable (0-19 years). Next, all patients with non-Hodgkin lymphomas were identified. Patients with primary tumors at the GI site were included in the final analysis.

Covariate selection. Data on patient demographics (age at diagnosis, gender, race), tumor characteristics (site, stage, histology), treatment (surgical resection) and overall survival (OS) were retrieved. Tumor histology was consolidated into four groups using ICD (international classification of diseases) oncology codes and based on similar histopathological and clinical features. The groups consisted of diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, extra nodal marginal zone lymphoma (EMZL) and "others". Due to very small number of cases with follicular, small lymphocytic lymphoma, peripheral T-cell lymphoma and "NHL not

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otherwise specified" (NOS), these tumors were consolidated in "others" category.

For disease stage, the seer variable "Summary Stage" was used. According to this variable, disease stage is classified in three stages. "Localized disease" included tumors limited to the site of origin. "Regional disease" included tumors with extension beyond the primary organ into the surrounding structures or lymph nodes. "Distant disease" included tumors with distant metastasis. Overall survival was defined as time interval from the time of initial diagnosis to the date of last contact (or the date of death if the patient was deceased).

Statistical analysis. Mean [SD (standard deviation)] and proportions were reported for continuous and categorical variables, respectively. Chi-square test and independent sample *t*-test were used for comparisons between groups. Overall survival (OS) rates were estimated using Kaplan–Meier (KM) analysis and evaluated using the log-rank test. Multivariate logistic regression was performed to identify predictors of survival. The analysis was conducted using Statistical Package for the Social Sciences Software (SPSS v.23.0, IBM Corp, USA). A p-value of ≤0.05 was considered as statistically significant. Subset analysis was conducted after stratifying patients based on tumor site, stage, histology and receipt of surgical resection.

Results

Baseline characteristics. A total of 452 cases were identified. Tumor characteristics are presented in Table I. The mean age was 11.0 (±5.1) years. The tumors predominantly affected white race and males (84.1% and 76.5%, respectively). The majority of tumors were noted in the small bowel (SB) (47.6%), followed by large bowel (LB) (28.5%) and the stomach (10.0%). In the SB and the LB, respectively, ileum and cecum were the most common sites of tumor involvement. Overall, the most common histological subtype at all locations was Burkitt lymphoma (51.8%), followed by diffuse large B-cell lymphoma (DLBCL) (26.1%).

Characteristics stratified by tumor site. On stratification by tumor site (Table II), the following differences were noted. Patients with gastric tumors were diagnosed at a later age compared to other sites (p=0.012). At all sites, tumors predominantly affected males, however, in stomach, equal gender predisposition was observed. Burkitt lymphoma was the predominant histological subtype at all locations except for stomach, where "other histology" was most frequent (p=0.053). Furthermore, almost one third of tumors in the stomach and "other location" presented with distant disease, whereas tumors in small bowel and large bowel mainly comprised of loco-regional disease (p<0.001). Finally, >80% of small and large bowel tumors received surgical resection whereas only 15% of gastric tumors underwent surgery (p<0.001).

Outcomes. Mean overall survival (OS) of the entire cohort was 33,33 years with a 5-yr, 10-yr and 30-yr survival rate of 86%, 86% and 79%, respectively (Table III). Large bowel tumors had the best long-term survival rates whereas, gastric tumors had the worst (30-yr survival rate 83% and 73%, respectively). Similarly, 30-yr survival rates for patients with Burkitt lymphoma were superior compared to DLBCL and other histologies (83%, 77% and 70%, respectively). Overall, 328 (72.6%) patients received surgery. No significant survival difference was noted between patients who underwent surgery and those who did not.

Multivariate cox regression analysis showed no survival benefit of surgical resection after adjusting for age, gender, race, histology, tumor site and stage (Table IV).

Table I. *Baseline characteristics (n=452).*

Variable	N (%)
Age at diagnosis, mean (SD)	11.0 (5.1)
Male gender	346 (76.5%)
White race	380 (84.1%)
Tumor site	
Small bowel (MC=ileum)	215 (47.6%)
Large bowel (MC=cecum)	129 (28.5%)
Stomach	45 (10.0%)
Others*	63 (13.9%)
Tumor histology	
Burkitt	234 (51.8%)
DLBCL	118 (26.1%)
EMZL	16 (3.5%)
Others*	84 (18.6%)
Stage (SEER)	
Localized	121 (26.8%)
Regional	101 (22.3%)
Distant	67 (14.8%)
Unknown	163 (36.1%)

*Appendix=21, anorectal=8, esophagus=2, liver=12, pancreas=6, NOS/Overlapping=14.

Discussion

In this study, we reported the largest dataset to date for pediatric non-Hodgkin's lymphoma primarily arising in the GI tract. In our analysis, we observed that the majority of these tumors were noted in the small bowel, with Burkitt lymphoma as the major histological subtype. Most of these tumors present at loco-regional stage with the exception of gastric tumors, one third of which present with distant disease. Overall survival rates for tumors in the large bowel were higher than other sites. No significant survival difference was noted between patients who underwent surgery and those who did not. These results are consistent with previous reported series on pediatric PGINHL (7, 8).

We also compared our results with primary GI lymphomas overall, reported previously by Shannon *et al*. (5) and others (Table V). Overall, the most common tumor site of involvement of these tumors was the stomach, compared to

Table II. *Characteristics of patients, stratified by tumor site.*

Variable	Tumor site				
	Stomach	Small bowel	Large bowel	Others	*p*-Value
No. of cases	45	215	129	63	
Age, mean (SD)	13.0 (4.9)	10.5 (5.0)	11.0 (5.1)	11.7 (5.02)	0.012
Male gender	24 (53.3%)	166 (77.2%)	108 (83.7%)	48 (76.2%)	0.001
White race	35 (77.8%)	181 (84.2%)	112 (86.8%)	52 (82.5%)	0.708
Disease stage					
Loco-regional	17 (63.0%)	105 (83.3%)	67 (76.1%)	33 (68.8%)	0.053
Distant	10 (37.0%)	21 (16.7%)	21 (23.9%)	15 (31.3%)	
Tumor histology					
DLBCL	14 (31.1%)	55 (25.6%)	28 (21.7%)	21 (33.3%)	0.001
Burkitt	11 (24.4%)	115 (53.5%)	85 (65.9%)	23 (36.5%)	
Others	20 (44.4%)	45 (20.9%)	16 (12.4%)	19 (30.2%)	
Surgical resection	7 (15.6%)	184 (85.6%)	107 (82.9%)	30 (47.6%)	0.001

Table III. *Overall survival, stratified by tumor site, stage, histology and surgery.*

Variable	n	5-year OS	10-year OS	30-year OS
All patients	452	86%	86%	79%
Tumor Site				
Large bowel	129	88%	88%	83%
Small bowel	215	87%	86%	77%
Stomach	45	73%	73%	73%
Other*	63	89%	89%	89%
Stage				
Localized	121	95%	95%	94%
Regional	101	93%	93%	90%
Distant	67	87%	87%	83%
Histology				
Burkitt lymphoma	234	88%	88%	83%
DLBCL	118	90%	89%	77%
Other histology	84	75%	75%	70%
Surgery				
Yes	328	88%	87%	77%
No	124	85%	85%	81%

*Appendix=21, anorectal=8, esophagus=2, liver=12, pancreas=6, NOS/Overlapping=14.

Table IV. *Multivariate model for overall survival.*

Variable	Hazards ratio	95% Confidence interval	*p*-Value
Age at diagnosis	1.07	0.98-1.17	0.141
Male (*vs.* Female)	1.49	0.46-4.81	0.513
White (*vs.* non-White)	1.04	0.35-3.09	0.940
Histology			
Other (ref)	--	--	0.359
DLBCL	0.55	0.16-1.83	
Burkitt	0.45	0.15-1.36	
Location			
Other (ref)	--	--	0.799
Stomach	1.53	0.27-8.76	
Small bowel	1.55	0.40-6.04	
Large bowel	0.98	0.22-4.43	
Distant disease (*vs.* locoregional)	2.27	0.91-5.64	0.079
Surgery (*vs.* no surgery)	1.35	0.41-4.43	0.616

small intestine noted in the pediatric group in our study. In addition, DLBCL is more common overall however, in children, Burkitt lymphoma was the most frequent histological variant. Moreover, a large proportion of the pediatric group underwent surgical resection (73% *vs.* 47% overall). Children with primary pediatric lymphoma also demonstrated superior survival compared to adults (5-yr OS 86% *vs.* 36%).

There are several potential limitations to consider with the present study. SEER database lacks information on several important variables including clinical presentation, diagnostic modalities, the use of chemotherapy and immunotherapy. This is important because both chemotherapy and immunotherapy are important in management of patients with primary GI lymphoma and data on the use of these regimens could have helped to validate some of our current treatment strategies. Also, even though data on receipt of surgical resection was available, information on emergent *vs.* palliative resection, extent of surgical resection and surgical complications was not available. In addition, no data on tumor size, extension, grade, modified Ann Arbor staging for GI lymphomas and nodal metastasis was found in the SEER database. Furthermore, the inherent limitations of using a population-based database including reporting errors, misdiagnosis and miscoding, might potentially exist in this study.

Table V. *Comparison of pediatric GI lymphomas with GI lymphomas overall in the SEER database.*

Variable	Pediatric data	Adult data
Similarities		
Race	Predominantly white (84%)	Predominantly white (84%)
Gender	Mostly male (76%)	Majority male (60%)
Disease stage	85% loco-regional	85% loco-regional
Differences		
Tumor site	1. Small intestine (48%) 2. Large intestine (29%) 3. Stomach (10%)	1. Stomach (50%) 2. Small intestine (29%) 3. Large intestine (16%)
Tumor histology	1. Burkitt (52%) 2. DLBCL (26%) 2. Follicular (11%)	1. DLBCL (63%)
Received surgical resection	73%	47%
Survival	5-yr OS 86%	5-yr OS 36%

Despite all these limitations, this database remains a valuable source in studying rare cancers such as GI lymphomas and provides the larger sample size to study the natural history of these cancers. More studies, however, are needed to validate findings of this study and also to define treatment regimens.

Conclusion

This is the largest series of primary pediatric GI lymphomas to be reported. Based on our results, these tumors are very rare in the pediatric population and are more common in whites and males, most commonly Burkitt lymphoma in the small bowel. Our analysis demonstrated no benefit of surgical resection which further reiterates that chemotherapy and immunotherapy are the primary modalities. To determine best practice treatment algorithms, a multicenter prospective study including different treatment modalities would help to better understand optimal management.

Conflicts of Interest

All Authors declare that they have no conflicts of interest and no financial disclosures to report regarding this study.

Authors' Contributions

The Author BN participated in study conception and writing; BN, AG and SJ participated in data analysis and writing; AG participated in study design, data interpretation and critical revision of the article.

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