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ORIGINAL ARTICLE

Surgical Management of Small Bowel Lymphoma

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Abstract

Background Primary small bowel non-Hodgkin's lymphoma is a rare disease representing 2% of small intestine malignancies. There is limited data delineating the optimal treatment for these heterogeneous tumors. We aim to examine relationships between different treatment modalities and surgical outcomes in patients with small bowel lymphoma.

Materials and Methods Patients diagnosed with stage I–III small bowel lymphoma in 2004–2015 who underwent surgery were identified in the National Cancer Database. Two cohorts were created based on systemic chemotherapy treatment status. The primary outcome was overall survival. An adjusted Cox proportional hazards model was used to evaluate the impact of treatment strategy on survival.

Results 2283 patients met inclusion criteria Of these patients, 826 patients (36%) underwent surgical resection alone, and 1457 patients (64%) underwent resection with systemic chemotherapy. Chemotherapy was associated with improved overall survival in unadjusted (5-year overall survival,
55% versus 70%) and adjusted analysis (HR 0.54, 95% CI 0.47–0.63, $p < 0.001$).

Discussion Patients with small bowel lymphoma have a low five-year overall survival after surgery. Chemotherapy is associated with improved survival, although one third of patients do not receive this therapy. Several other clinical factors are identified that are also associated with overall survival, including histology subtype, margin status, age, and medical comorbidities. This information can help with prognostication and potentially aid in treatment decision-making.

Keywords Small intestine · Extranodal lymphoma · Treatment

Introduction

Primary non-Hodgkin's lymphomas arising from gastrointestinal extranodal sites are a rare entity. Primary small bowel malignancies comprise only approximately 2% of all gastrointestinal cancers, and about 20% of these are primary lymphomas.[1] While they are rare, the incidence of primary small bowel lymphomas has been increasing in the USA.[2, 3] Though they have a low incidence, primary small bowel lymphomas present with a wide range of histologies.[4, 5] Because of this, there is little data regarding treatment outcomes for this disease entity.

In the past, studies that have evaluated primary gastrointestinal lymphomas often treated different gastrointestinal primary sites as a single disease entity; however, the treatment patterns and survival rates of lymphomas arising from different sites (e.g., gastric, small bowel, colon) can vary considerably.[4, 6] Given the heterogeneity of the disease in conjunction with its relative rarity, prior reports tend to be limited by low patient numbers, represent single institution studies, and often combine results from patients with different gastrointestinal primary sites.[4, 7–9]

While chemotherapy has been the mainstay of treatment for extranodal lymphomas, the role of surgery and surgical outcomes have been less clear.[10] Surgical resection can palliate symptoms related to mass effect, provide tissue needed for definitive diagnoses, and potentially serve as definitive therapy in cases of limited disease.[10] However, the benefit of

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surgical resection has not been definitively shown, and concerns about potential operative and postoperative complications remain.[9, 11] Studies that examine the survival outcomes of treatment of small bowel lymphoma with surgical resection alone compared with surgical resection and chemotherapy combined have shown variable results.[7, 8] For example, Li et al. reported in an institutional experience of 40 gastrointestinal lymphoma patients, 14 of whom had small bowel primary sites, that postoperative chemotherapy improved event-free survival compared with surgery alone, but no benefits in overall survival were seen.[7] Ibrahim et al. reported an experience of intestinal lymphoma with 66 patients, 37 of whom had a small bowel primary site; in this study, surgery was associated with improved overall survival.[8] In a review of primary gastrointestinal lymphomas arising from both small and large bowel sites, the majority of patients were treated with multimodal therapy but only 43% of the reviewed studies reported survival benefit including surgical resection as part of the treatment.[6]

To date, there have been no large randomized controlled trials examining surgical outcomes in patients with primary small bowel lymphomas, and evidence supporting best treatment practices for this disease is limited. In this context, we sought to fill an existing gap in knowledge on surgical outcomes by examining the survival and treatment effects of surgery in patients with primary non-Hodgkin's lymphomas arising from the small bowel using a generalizable, national database.

Materials and Methods

Data Source

For this study, the National Cancer Database (NCDB) Participant Use Data Files were queried between the years 2004 and 2015. The NCDB is an oncology database that is sponsored by the American College of Surgeons together with the American Cancer Society. The database collects relevant de-identified clinical data from patients with malignant diseases from over 1500 Commission on Cancer (CoC) accredited institutions nationwide. Data is retrieved by local extractors from over 34 million historical patient files and represent over 70% of annual cancer diagnoses made in the USA. Further details on NCDB methodology for data collection and auditing have been described in greater detail previously.[12] The data were used under a data use agreement for this study. The study was reviewed and deemed exempt by the Brigham and Women's Hospital Institutional Review Board.

Patient Cohort

Adult patients diagnosed with lymphoma of the small bowel were identified using the International Classification of Diseases for Oncology (ICD-O) codes. Those with clinical stage I–III disease with histologic subtypes of large B cell (ICD-O 9680), marginal B cell (ICD-O 9699), follicular (ICD-O 9690, 9695, 9691, 9698), T cell (ICD-O 9702, 9717, 9714, 9719, 9827), and Burkitt cell (ICD-O 9687) were included. Patients who did not undergo surgical resection of the primary site were deemed ineligible to undergo chemotherapy, or were missing survival or chemotherapy treatment data were excluded (Fig. 1).

Variable Selection

Patient data including patient age, sex, race, income level, insurance status, urban/rural location, education level, and travel distance were collected. Clinical data including Charlson comorbidity score, radiation and chemotherapy treatment, surgical margin status, and histology were queried. Finally, treatment facility details were also collected, including facility region, facility type (including Academic Programs, Community Cancer Programs, Comprehensive Community Cancer Programs, and Integrated Network Cancer Programs),[1] and treatment travel distance. The primary outcomes of interest were overall survival, and predictors of improved survival.

Statistical Analysis

Descriptive statistics are presented using percentages, or medians with interquartile range. Differences in characteristics between groups were assessed with Pearson's chi-square tests for categorical variables. Overall survival was assessed using the Kaplan-Meier method, and differences in survival between patients who underwent chemotherapy compared with those who did not were evaluated with log-rank tests. A Cox proportional hazards model was used to identify predictors of overall survival. Variables were included in the model if the p value was < 0.1 on the univariable screen. Missing data was categorized as unknown. Two-tailed p values of 0.05 were considered significant. All statistical analysis was performed with Stata Statistical Software, Version 14.1 (StataCorp, College Station, Tx, StataCorp LLC).

[1] Academic cancer programs: facilities that participate in post-graduate medical education in four or more areas, including internal medicine and general surgery. Community cancer programs (CCP): facilities which see between 100 and 500 cancer diagnoses annually and offer access to a full range of diagnostic and therapeutic options. Comprehensive community cancer programs (CCCP): similar to CCPs; however, they see over 500 cancer diagnoses annually. Integrated network cancer programs (INCP): facilities that are part of a joint venture with multiple facilities providing integrated cancer care with full services.

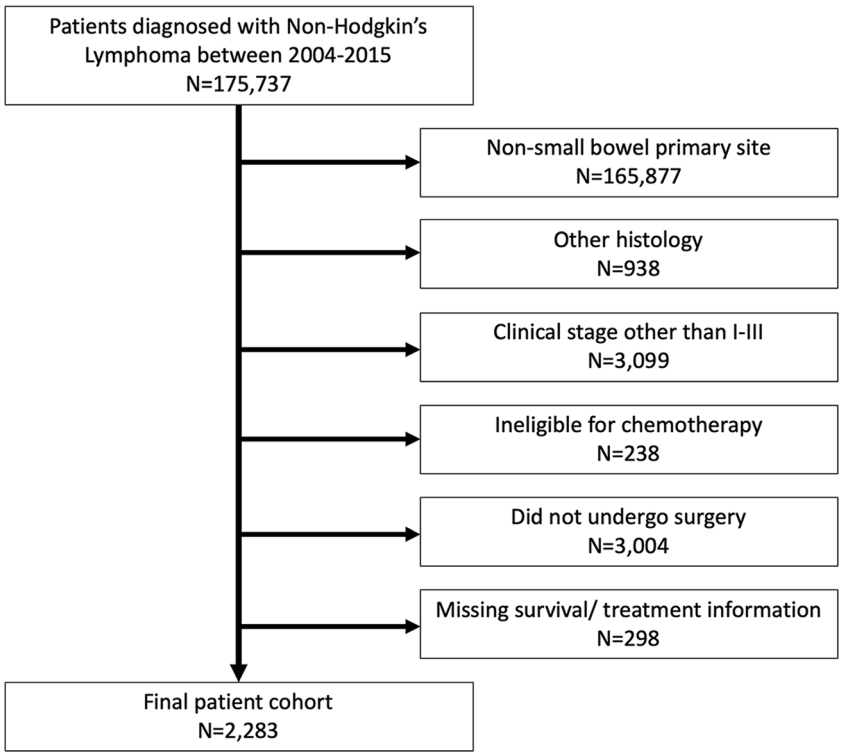

Fig. 1 Patient selection flowchart to identify final patient cohort

Results

Patient Characteristics

2283 patients met inclusion criteria. Of these, 826 (36.2%) did not undergo chemotherapy, while 1457 (63.8%) did. Of the patients, 1218 (53.4%) had large B cell histology, and the median age across both groups was 56 (Interquartile Range 56–77). Patients who underwent chemotherapy tended to be younger, male, have fewer medical comorbidities, have private insurance, and have large B cell histology ($p < 0.05$). No significant differences were seen in race, income level, education level, patient region, travel distance, or year of diagnosis between the two groups (Table 1).

Treatment Characteristics and Short-Term Outcomes

The majority of patients (> 96%) in both groups did not undergo radiation treatment. In the chemotherapy group, 83.2% of patients underwent adjuvant chemotherapy treatment, 2.2% underwent neoadjuvant treatment, 0.7% of patients underwent both, and 14.9% of patients had an unknown treatment sequence. Significantly more patients who received chemotherapy had documented positive surgical margins (9.5%) compared with those who did not receive chemotherapy treatment (7.0%), $p = 0.041$. There were no significant differences in 30-day postoperative readmission rates or postoperative length of stay ($p > 0.05$) (Table 2).

Survival

In unadjusted analysis, five-year overall survival was 65%. Overall survival was significantly improved in patients who did undergo chemotherapy treatment (5-year survival, 69.9%, 95% CI (62.4%–66.7%)) compared with those who did not (5-year survival, 55.2%, 95% CI (51.4%–58.8%)), $p < 0.001$ (Fig. 2). When stratified by histology, follicular histology showed improved survival (5-year survival 65.3%, 95% CI (59.0–70.9%)), whereas T cell histology showed lowest survival (5–year survival 16.5%, 95% CI (10.2%, 24.2%)). A 5-year overall survival for the remaining histologies were as follows: large B cell 42.2%, 95% CI (37.8%–46.3%), marginal B cell 58.3%, 95% CI (47.5%–67.6%), Burkitt 62.8%, 95% CI (48.8%–78.0%). Survival was significantly different between histologies ($p < 0.001$) (Fig. 3). After adjusting for appropriate patient sociodemographic, clinical, and treatment facility factors in the Cox proportional hazards model, chemotherapy treatment was associated with significantly improved survival (HR 0.54, 95% CI (0.47, 0.63), $p < 0.001$) (Fig. 4). Additional factors associated with improved survival included histology subtypes of marginal B cell and follicular lymphoma ($p < 0.001$ for both). Factors associated with significantly worse survival included increased age, more medical

Table 1 Patient characteristics

Variable	No chemotherapy ($n = 826$)	Chemotherapy ($n = 1457$)	p value
Age			< 0.001
≤50	84 (10.2%)	281 (19.3%)	
51–60	130 (15.7%)	307 (21.1%)	
61–70	178 (21.5%)	365 (25.1%)	
71–80	191 (23.1%)	348 (23.9%)	
81–90	243 (29.4%)	156 (10.7%)	
Sex			< 0.001
Male	454 (55.0%)	919 (63.1%)	
Female	372 (45.0%)	538 (36.9%)	
Race			0.27
White	714 (86.4%)	1217 (83.5%)	
Black	42 (5.1%)	80 (5.5%)	
Hispanic	37 (4.5%)	88 (6.0%)	
Asian	24 (2.9%)	55 (3.8%)	
Other	7 (0.8%)	8 (0.5%)	
Unknown	2 (0.2%)	9 (0.6%)	
Charlson comorbidity score			0.023
0	577 (69.9%)	1088 (74.7%)	
1	176 (21.3%)	276 (18.9%)	
≥2	73 (8.8%)	93 (6.4%)	
Insurance status			0.023
Private	577 (69.9%)	1088 (74.7%)	
Medicaid	176 (21.3%)	276 (18.9%)	
Medicare	73 (8.8%)	93 (6.4%)	
Uninsured	19 (2.3%)	44 (3.0%)	
Unknown	8 (1.0%)	12 (0.8%)	
Median income			0.16
< 38,000$	119 (14.4%)	214 (14.7%)	
38–47,999$	162 (19.6%)	337 (23.1%)	
48–62,999$	241 (29.2%)	381 (26.1%)	
> 63,000$	297 (36.0%)	519 (35.6%)	
Unknown	7 (0.8%)	6 (0.4%)	
Education (% no high school degree)			0.67
< 7%	240 (29.1%)	416 (28.6%)	
7–12.9%	276 (33.4%)	472 (32.4%)	
13–20.9%	185 (22.4%)	348 (23.9%)	
> 21%	119 (14.4%)	216 (14.8%)	
Unknown	6 (0.7%)	5 (0.3%)	
Facility type			< 0.001
Academic	228 (27.6%)	377 (25.9%)	
CCP[a]	96 (11.6%)	128 (8.8%)	
CCCP[b]	365 (44.2%)	615 (42.2%)	
INCP[c]	114 (13.8%)	216 (14.8%)	
Other/unknown program	23 (2.8%)	121 (8.3%)	
Region type			0.10
Metro	664 (80.4%)	1226 (84.1%)	
Urban	120 (14.5%)	162 (11.1%)	
Rural	15 (1.8%)	28 (1.9%)	
Unknown	27 (3.3%)	41 (2.8%)	
Facility location			< 0.001
New England	53 (6.4%)	78 (5.4%)	
Middle Atlantic	124 (15.0%)	195 (13.4%)	
South Atlantic	160 (19.4%)	261 (17.9%)	
East North Central	153 (18.5%)	230 (15.8%)	
East South Central	45 (5.4%)	87 (6.0%)	
West North Central	83 (10.0%)	126 (8.6%)	
West South Central	51 (6.2%)	101 (6.9%)	
Mountain	42 (5.1%)	67 (4.6%)	
Pacific	92 (11.1%)	191 (13.1%)	
Unknown	23 (2.8%)	121 (8.3%)	
Year of diagnosis			0.91
2004	59 (7.1%)	102 (7.0%)	
2005	55 (6.7%)	100 (6.9%)	
2006	54 (6.5%)	118 (8.1%)	
2007	68 (8.2%)	100 (6.9%)	
2008	55 (6.7%)	106 (7.3%)	
2009	79 (9.6%)	132 (9.1%)	
2010	81 (9.8%)	147 (10.1%)	
2011	80 (9.7%)	127 (8.7%)	
2012	68 (8.2%)	134 (9.2%)	
2013	76 (9.2%)	143 (9.8%)	
2014	77 (9.3%)	123 (8.4%)	
2015	74 (9.0%)	125 (8.6%)	
Distance to treatment facility			0.13
First tertile	495 (59.9%)	938 (64.4%)	
Second tertile	242 (29.3%)	384 (26.4%)	
Third tertile	84 (10.2%)	131 (9.0%)	
Unknown	5 (0.6%)	4 (0.3%)	
Lymphoma histology			<0.001
Large B Cell	285 (34.5%)	933 (64.0%)	
Marginal B Cell	161 (19.5%)	87 (6.0%)	
Follicular	296 (35.8%)	223 (15.3%)	
T cell	72 (8.7%)	122 (8.4%)	
Burkitt	12 (1.5%)	92 (6.3%)	

[a] Community Cancer Program

[b] Comprehensive Community Cancer Program

[c] Integrated Network Cancer Program

comorbidities, Medicaid insurance, lower level of education, positive margin status, and T cell histology ($p < 0.05$ for all) (Table 3).

Discussion

In this study, we demonstrate that systemic chemotherapy in addition to surgical resection of the primary site is associated

Table 2 Treatment characteristics and short-term outcomes

Variable	No chemotherapy ($n = 826$)	Chemotherapy ($n = 1475$)	p value
Radiation sequence			0.32
No radiation	805 (97.5%)	1405 (96.4%)	
Neoadjuvant	0 (0.0%)	4 (0.3%)	
Adjuvant	15 (1.8%)	37 (2.5%)	
Sequence unknown	6 (0.7%)	11 (0.8%)	
Systemic chemotherapy sequence			< 0.001
No systemic chemotherapy	709 (99.6%)	0 (0.0%)	
Neoadjuvant	0 (0.0%)	27 (2.2%)	
Adjuvant	0 (0.0%)	1032 (82.2%)	
Both	0 (0.0%)	9 (0.7%)	
Sequence unknown	3 (0.4%)	187 (14.9%)	
Surgical margins			0.041
Negative	411 (49.8%)	660 (45.3%)	
Positive	58 (7.0%)	138 (9.5%)	
Not reported/unknown	357 (43.2%)	659 (45.2%)	
30 day readmission	45 (5.4%)	77 (5.3%)	0.13
Postoperative length of stay (median days, IQR)	6 (4, 9)	6 (5, 9)	0.13

with significantly improved survival in patients with non-metastatic primary small bowel lymphoma compared with surgical resection alone. This information should be considered when counseling patients regarding treatment options for primary small bowel lymphomas.

We report a range of histologic subtypes in our patient cohort, the most common being large B cell lymphoma. This is in accordance with prior studies evaluating primary gastrointestinal lymphomas.[5, 13, 14] Additionally, the survival differences seen in both our unadjusted and adjusted analysis are concordant with what has been previously shown in other studies evaluating histologic differences among gastrointestinal primary lymphomas. In particular, follicular histology has been known to have an indolent clinical course in gastrointestinal non-Hodgkin's lymphomas overall compared with other histologies, and small bowel primary sites have been associated with improved survival compared with other gastrointestinal sites.[15] We found in our cohort that follicular histology demonstrated higher overall survival in unadjusted analysis and also was a significant predictor of survival in the Cox

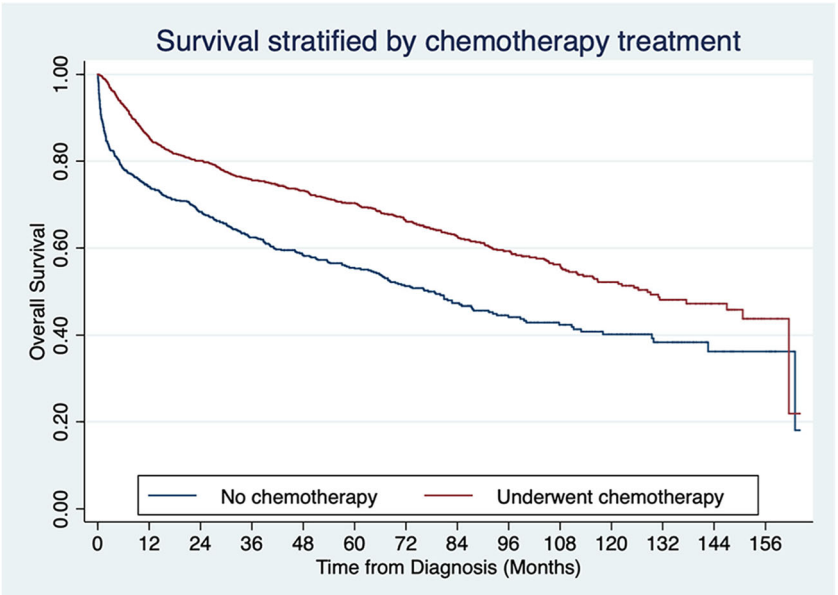

Fig. 2 Overall survival stratified by chemotherapy treatment: chemotherapy versus no chemotherapy

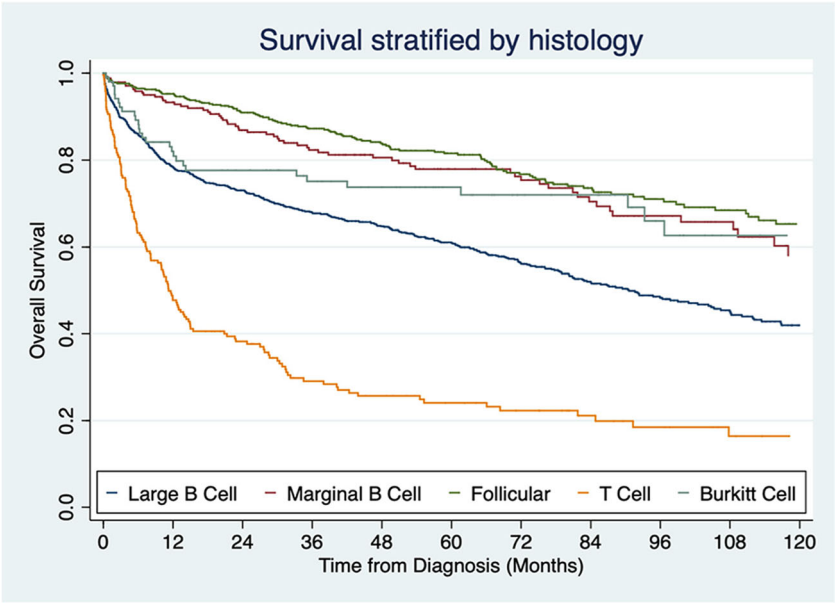

Fig. 3 Overall survival stratified by histology: follicular, marginal B cell, burkitt, large B cell, and T cell

proportional-hazards model. Similarly, our results showed that T cell histology was associated with worse survival in both unadjusted and adjusted analyses—these results mirror those of a small retrospective study reported by Yin et al. that compared survival of primary small bowel lymphoma with B cell and T cell histologies.[16]

With respect to treatment outcomes, we noted inconsistent reporting of margin status in both groups, with over 40% of patients in both cohorts having unknown margin status. 49.8% of patients in the current study who did not receive chemotherapy and 45.3% of patients who did undergo systemic treatment had documented R0 resection with negative surgical margins reported, but only 7% of patients in the no chemotherapy group and 9.5% of patients in the chemotherapy group had positive margins reported. This pattern differs than that reported by Hong et al., who found in 62 patients who underwent resection for primary small bowel lymphoma that in patients who also underwent chemotherapy, 75% had R0 resections, whereas only 42.9% of patients who did not receive chemotherapy had R0 resections.[9] This difference may be related to the fact that we excluded patients with stage IV disease in our cohort, and operative interventions were performed with intent in resecting the primary site of disease. Many prior studies evaluating differences in treatment outcome focused on surgical compared with medical treatments alone, or report results of mixed primary gastrointestinal sites.[9, 14, 17, 18] In a small study of 40

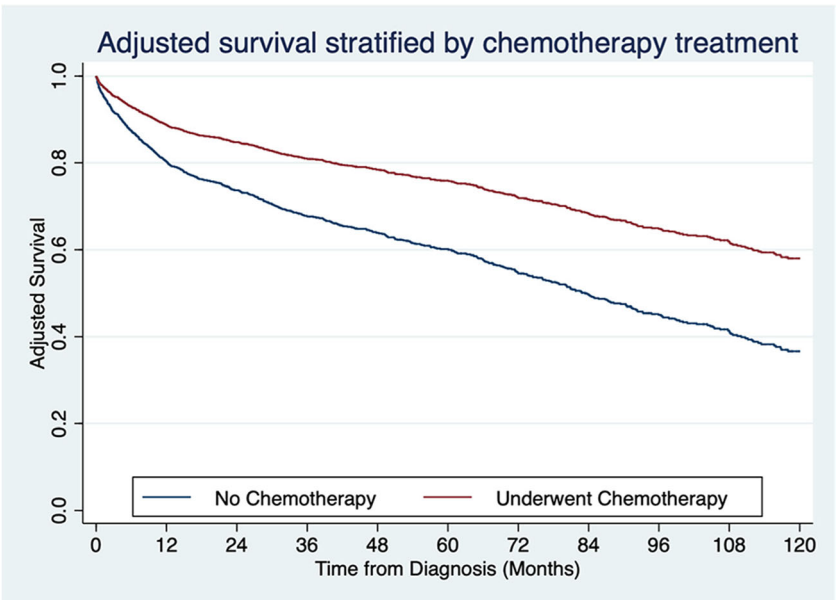

Fig. 4 Adjusted overall survival stratified by chemotherapy treatment: chemotherapy versus no chemotherapy. Curves adjusted for age, race, Charlson comorbidity score, insurance type, facility type, margin status, histology type, and education level

Table 3 Cox proportional hazards model—predictors of overall survival

Variable	Hazard ratio	95% confidence interval	*p* value
Chemotherapy			
No chemotherapy	ref		
Received chemotherapy	0.54	(0.47, 0.63)	< 0.001
Age			
≤50	ref		
51–60	1.09	(0.74, 1.60)	0.661
61–70	1.87	(1.29, 2.70)	0.001
71–80	2.45	(1.67, 3.59)	< 0.001
81–90	4.31	(2.93, 6.35)	< 0.001
Race			
White	ref		
Black	0.77	(0.54, 1.08)	0.131
Hispanic	0.77	(0.54, 1.09)	0.143
Asian	0.77	(0.51, 1.15)	0.202
Other	0.84	(0.27, 2.63)	0.768
Charlson comorbidity score			
0	ref		
1	1.25	(1.07, 1.47)	0.006
≥ 2	1.80	(1.44, 2.24)	< 0.001
Insurance			
Private	ref		
Medicaid	1.88	(1.32, 2.68)	< 0.001
Medicare	1.21	(0.98, 1.50)	0.076
Uninsured	1.08	(0.62, 1.87)	0.792
Education (% no high school degree)			
< 7%	ref		
7–12.9%	1.12	(0.94, 1.33)	0.215
13–20.9%	1.15	(0.95, 1.39)	0.161
> 21%	1.30	(1.04, 1.62)	0.023
Unknown	1.57	(0.50, 4.94)	0.442
Facility type			
Academic	ref		
CCP[a]	1.05	(0.82, 1.33)	0.702
CCCP[b]	1.04	(0.88, 1.23)	0.667
INCP[c]	0.95	(0.76, 1.19)	0.668
Other/unknown	0.70	(0.41, 1.20)	0.197
Margin status			
Negative	ref		
Positive	1.56	(1.23, 1.97)	< 0.001
Not reported/unknown	1.21	(1.05, 1.40)	0.008
Histology type			
Large B Cell	ref		
Marginal B Cell	0.39	(0.30, 0.52)	< 0.001
Follicular	0.34	(0.28, 0.42)	< 0.001
T cell	2.75	(2.26, 3.35)	< 0.001
Burkitt	1.09	(0.74, 1.60)	0.675

[a] Community Cancer Program

[b] Comprehensive Community Cancer Program

[c] Integrated Network Cancer Program

patients of mixed colorectal and small intestine primary sites, Li et al. reported that surgery in combination with chemotherapy had significantly improved survival when compared with surgery alone.[7] Though a different gastrointestinal site, Maguire et al. reported contemporary treatment outcomes of primary colonic lymphomas and found that surgical intervention in conjunction with chemotherapy conferred survival benefit over resection alone.[19] Our findings correlate with these other reports of varying design.

Our study findings must be viewed within the context of our study design. While the NCDB captures over 70% of new cancer diagnoses across the nation, it only collects data from CoC accredited institutions whose practices may not be reflective of all facilities treating patients with rare cancers in the USA. Additionally, there are limitations on the variables available in the NCDB. Details on chemotherapy regimen or chemotherapy agents administered, reasons for why chemotherapy was not given, and why certain systemic chemotherapy sequences were prescribed are not available, nor are outcomes of chemotherapy treatment reported (i.e., clinical response). Similarly, only overall survival is recorded, and we are unable to calculate disease-specific survival. Staging of extranodal lymphomas has also been a controversial topic in the past, and the NCDB does not report the system of staging used for each patient.[20] Finally, this study is retrospective in nature. Despite this, our study has many strengths. This is one of the largest studies to evaluate the impact of systemic chemotherapy and surgical resection compared with surgical resection alone of primary small bowel lymphoma, a rare and heterogeneous disease, using contemporary data from a national database.

Conclusion

Patients with primary non-Hodgkin's lymphoma of the small bowel who undergo surgery in conjunction with chemotherapy have improved survival compared with those who undergo resection alone. However, approximately one third of patients who undergo surgical resection do not receive chemotherapy treatment. These results should be considered when discussing treatment options with patients with this rare disease entity, and can be an important tool for patient counseling and prognostication.

Author Contributions All authors had substantial contributions to design of work, drafted work, made final approval, and agreed to be accountable for all aspects of the work.

Compliance with Ethical Standards

Conflict of Interest The authors declared no conflict of interest.

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