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Primary Non-Hodgkin's Lymphoma of the Gallbladder: A Population-based Analysis

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Abstract. *Background/Aim: Primary Non-Hodgkin's lymphoma of the gallbladder (PNHL-GB) is extremely rare and data on clinical characteristics, optimal management and outcomes of these patients are limited to anecdotal reporting. We, therefore, sought to examine these patients using a population-based database. Materials and Methods: Surveillance, epidemiology, and end results (SEER) database was queried between 1973 and 2013. Results: One hundred and six cases with PNHL-GB were identified (mean age=70.5 ±15 years, whites 92%, male: female 1.03:1). The majority of patients had loco-regional disease (61%) and DLBCL histology (33%). Ninenty cases (85%) had undergone surgical resection, 6 (5.6%) received radiotherapy. Median overall survival (OS) of the entire cohort was 41 months with a 5-year survival rate of 40%. Patients receiving adjuvant RT had superior OS compared to surgery alone (140 ±27 vs. 86 ±16 months, respectively) and patients with DLBCL demonstrated lower survival compared to other histologies (13 vs. 53 months, respectively, p=0.034). Conclusion: Our study presents the largest dataset of PNHL-GB describing clinical features and outcomes of these patients in addition to summarizing the literature.*

Primary lymphomas are rare in the alimentary canal, representing approximately 1-4% of all gastrointestinal (GI) malignancies (1). Dawson *et al*. first described "primary gastrointestinal lymphoma" as a "predominantly GI tract lesion with no involvement of the peripheral nodes/ mediastinal nodes/liver or spleen and a normal white cell count and differential" (2). Among primary GI lymphomas, the gastric location is the most common site involved followed by small intestine and large intestine, respectively (3). Primary non-Hodgkin's lymphoma of the gallbladder (PNHL-GB) is exceedingly rare. The management of these cases is based on anecdotal reports totaling approximately 30 cases. The available data on PNHL-GB is insufficient to understand the natural history of the disease including the clinico-pathological features and outcomes. We, therefore, sought to evaluate the clinical characteristics, treatment and survival outcomes of these patients utilizing a population-based database. In addition, we aim to summarize previously reported cases of PNHL-GB in the literature.

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Materials and Methods

Study population. We identified 22,497 cases of gallbladder cancer from the Surveillance, Epidemiology, and End Results (SEER) database (18 Regs Research Data, Nov 2015 Sub) between 1973-2013 using the primary code for gallbladder (C23.9) (4). Of those patients, all cases with non-Hodgkin's lymphoma (NHL) were identified using the World Health Organization (WHO) 2008 lymphoma classification (5). Only patients with histologically-confirmed primary cancers were included in the final analysis.

Covariate selection. Data on patient demographics (age at diagnosis, gender, and race), tumor characteristics (stage, histology), treatment (surgical resection, adjuvant radiotherapy (RT)) and overall survival were retrieved. Race was recorded into white and non-white (including Blacks, Asian/Pacific Islanders, and Native Americans). Disease stage was derived from SEER "Summary Stage" variable and included three categories. "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 (OS) was defined as time interval from the time of initial diagnosis to the date of the last contact (or the date of death, if the patient was deceased).

Statistical analysis. Continuous variables were compared with the ANOVA test and categorical variables were compared with the chi-square test. Overall survival rates were estimated using Kaplan-Meier (KM) analysis and evaluated using the log-rank test. The

Multivariate Cox-proportional hazards model was used to identify independent prognostic factors. The analysis was conducted using Statistical Package for the Social Sciences Software (SPSS v.17.0, IBM Corp, USA). A *p*-value of <0.05 was considered as statistically significant.

Results

Out of 22,497 cases with gallbladder cancer, 106 cases of PNHL-GB were identified. The mean age at diagnosis was 70.5 ±15 years. Patients were predominantly white (92%) with a male: female of 1.03:1. Diffuse large B-cell lymphoma (DLBCL) was the most common histological subtype (33%), followed by follicular lymphoma (FL) (16%) and extranodal marginal zone lymphoma (EMZL) (14.2%). The majority of patients (61.3%) had loco-regional disease at the time of diagnosis. Surgical resection was performed in 90 (85%) cases and out of these, five patients received adjuvant RT. Patient characteristics for the entire cohort are summarized in Table I.

Patients with FL were younger at diagnosis compared to patients with DLBCL/EMZL (65.7 *vs.* 70.3 years, respectively). They showed female preponderance (76.5%) and most had loco-regional disease (68.8%) at the time of diagnosis. DLBCL, the most common histological variant in this cohort (33%), predominantly affected males (68.6%) and had the highest proportion of cases (42.9%) that presented with distant spread at the time of diagnosis. EMZL patients showed equal gender distribution and had the highest proportion in non-white race (20%) amongst all histologies. The majority of cases with EMZL presented with loco-regional disease (93.3%). Patient characteristics stratified by tumor histology are summarized in Table II.

The median OS of the entire cohort was 41 months (95% confidence interval (CI)=21-61) with a 5-year survival rate of 40%. OS for patients with FL, DLBCL and EMZL was 53, 13 and 76 months, respectively (p=0.319). DLBCL patients had significantly lower survival compared to FL/EMZL patients combined (13 *vs.* 53 months, respectively, p=0.034, Figure 1a). Median survival of patients undergoing surgical resection was higher than those who did not receive surgery (42 months *vs.* 2 months, p=0.015) (Figure 1b). On stratification by stage, OS of patients with loco-regional disease who received surgery was 83±15 months compared to 16±6 months for those who did not undergo resection. OS for patients with distant disease who underwent resection was 84±14 months compared to 21±14 months for those who did not receive surgery.

For patients who received adjuvant RT, OS was 140±27 months compared to patients who underwent resection only (OS=86±16 months). No difference in OS was observed between whites *vs.* non-whites (p=0.318) and males *vs.* females (p=0.568). On multivariate analysis, increasing age at diagnosis was associated with increased hazards of death (HR 1.05, p<0.001), surgical resection had an overall protective effect (HR 0.03, p=0.007), while gender, race, tumor histology, and disease stage were not associated with OS (Table III). Overall, 63 deaths (59.4%) were noted in this cohort. Thirty deaths (47.6%) were related to the primary disease. Thirty-three (52.4%) patients died from other causes and the most common cause of mortality in this group was related to cardiovascular causes (n=11).

Table I. *Characteristics of patients with primary gallbladder lymphoma (n=106).*

Variable	
Age at diagnosis, mean (SD)	70.5 (15.3)
Male gender	54 (50.9%)
White race	97 (91.5%)
Tumor histology	
DLBCL	35 (33.0%)
Follicular lymphoma	17 (16.0%)
EMZL	15 (14.2%)
Others[a]	39 (36.8%)
Disease stage	
Localized	51 (48.1%)
Regional	14 (13.2%)
Distant	35 (33.0%)
Unknown	6 (5.7%)
Treatment	
Surgery	85 (80.2%)
Surgery + RT	5 (4.7%)
RT only	1 (0.9%)
No Surgery, no RT	11 (10.4%)
Unknown	4 (3.8%)
Overall survival	
Median (months)	42.3
1-year, 5-year	68%, 40%
Deaths	63 (59.4%)
Cause of death	
Lymphoma related	30 (47.6%)
Others	33 (52.4%)

DLBCL, Diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma. [a]Includes NHL not otherwise specified (n=10), mantle cell lymphoma (n=7), small B lymphocytic (n=6), Burkitt lymphoma (n=4) *etc.*

Discussion

Primary lymphomas of the gallbladder are extremely rare, representing around 0.1-0.2% of all malignant tumors of the gallbladder (6). Data on clinical characteristics, optimal management and outcomes of these tumors is extremely limited. Mitropoulos *et al.* identified 11 cases of PNHL-GB reported in the English literature and observed that these patients present a median age of 68 years with equal gender distribution. The most common-presenting complaint among these patients was abdominal pain (7). The largest dataset to

Table II. *Characteristics of patients with primary gallbladder lymphoma, stratified by common histological subtypes (n=67).*

Variable	DLBCL	FL	EMZL	*p*-Value
No. of cases	35 (33%)	17 (16%)	15 (14.2%)	
Age at diagnosis, mean (SD)	70.3 (16.7)	65.7 (11.3)	70.3 (12.7)	0.539
Male gender	24 (68.6%)	4 (23.5%)	8 (53.3%)	0.009
White race	32 (91.4%)	16 (94.1%)	12 (80%)	0.373
Disease stage				
Loco-regional	20 (57.1%)	11 (68.8%)	14 (93.3%)	0.042
Distant		15 (42.9%)	5 (31.3%)	1 (6.7%)
Surgical resection	29 (82.9%)	14 (87.5%)	15 (100%)	0.235
Overall survival				
Median (months)	13	53	76	0.106
1-year, 5-year	51%, 29%	94%, 47%	78%, 54%	
Deaths	24 (68.6%)	7 (41.2%)	6 (40%)	0.071
Lymphoma as cause of death	14 (58.3%)	4 (57.1%)	3 (50%)	0.934

date was provided by Mani *et al*., who described their single-Institution series of 13 patients with primary gallbladder lymphoma. In addition, they also performed a comprehensive review of the literature and summarized previously reported cases (6). They observed that these cancers were primarily noted in females and most patients presented with symptoms mimicking cholecystitis. In their series, DLBCL was the most common histological variant, followed by EMZL and FL, respectively. Patients with DLBCL and EMZL were older (mean age 75.8 years) at the time of diagnosis versus other lymphoma subtypes (mean age 47 years) and were more likely to present with gallstones.

Our study represents the largest series of patients with PNHL-GB. We observed that this cancer predominantly affects white males, usually in the seventh decade of life. Most patients have loco-regional disease at the time of diagnosis. We also observed certain differences amongst different histological subtypes of PNHL-GB. In addition, we noted that patients with DLBCL had lower overall survival compared to FL and EMZL. Furthermore, patients who underwent resection survived longer than those who did not receive surgery (both for the whole patient cohort and after stratification by stage). Finally, our results demonstrate that patients who received adjuvant RT appeared to survive longer than those who received surgery alone.

The results of this study are very similar to previously reported studies of other primary GI non-Hodgkin lymphomas. The largest dataset of patients with primary GI non-Hodgkin lymphomas was reported by Shannon et al who analyzed 16,129 patients using the SEER database (3). They observed that primary GI NHL primarily affects white males, and the majority of cases are diagnosed after 65 years of age. DLBCL was the most common histological variant, followed by FL. In their series, the gastric location was the most common site and included 49.7% of identified cases, while 28.5% occurred in the small intestine and 16.4% in the large intestine. Among patients for whom staging information was available, 44.3% had localized disease (*vs*. 67% in our series). Overall median survival was 25 months with a 5-year survival rate of 35.6% (*vs*. 42 months and 40% in our patients). In their series, female gender and follicular cell histology were associated with improved survival. None of these factors had effect on survival in our small analysis of gallbladder lymphoma patients. They noted higher survival in patients who received adjuvant RT *vs*. resection alone (median 69 months *vs*. 36 months, respectively), possibly indicating a role of adjuvant RT in primary GI lymphomas.

Table III. *Multivariate model for overall survival in patients with primary gallbladder lymphoma.*

	Hazards ratio	95% Confidence Interval	*p*-Value
Age at diagnosis	1.05	1.02-1.07	<0.001
Female (*vs*. male)	0.91	0.52-1.60	0.752
White (*vs*. non-white)	1.06	0.32-3.50	0.919
DLBCL (*vs*. all other histologies)	1.34	0.77-2.32	0.301
Distant disease (*vs*. loco-regional)	1.67	0.94-2.95	0.079
Surgery (*vs*. no surgery)	0.32	0.14-0.73	0.007

We also summarized PNHL-GB cases previously described in the literature (Table IV) (6-20). We found that most cases of PNHL-GB are diagnosed incidentally in cholecystectomy specimens (7). Few case reports have described the use of fine-needle aspiration as a potential preoperative diagnostic tool (21). In addition, certain radiological features have been observed with different histological subtypes that can aid in preoperative diagnosis. For example, high-grade lymphomas such as DLBCL manifest as a bulky solid mass within the

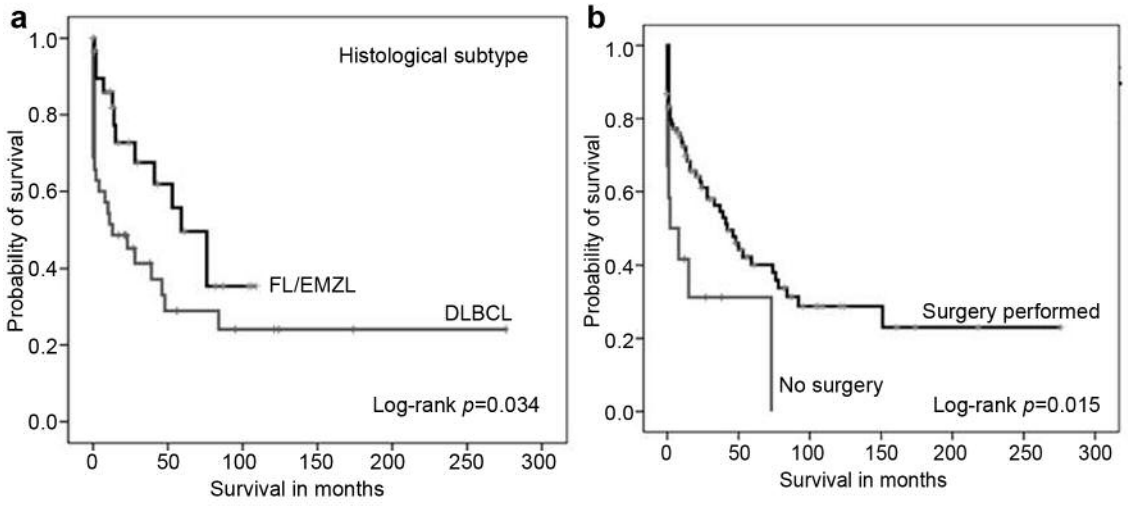

Figure 1. *Kaplan–Meier survival curve for overall survival by (a) DLBCL vs. FL/EMZL histology (median survival 13 months vs. 53 months, p=0.034); b): surgical resection vs. no resection (median survival 42 months vs. 2 months, p=0.015).*

Table IV. *Previously reported cases of primary NHL of the gallbladder.*

Authors	Year	No of cases	Age	Gender	Histology	Surgery	Chemo/RT	Outcome
Konishi	2016	1	77	F	PBL	None	Chemo	7m, D
Karia	2015	1	81	M	EMZL	C	None	--
Katiyar	2015	1	48	F	NHL, B-cell diffuse type	C	None	Died postoperatively
Acharya	2014	1	75	F	FL	C	None	6m, A
Psarras	2014	1	85	M	SLL	C	None	1yr, A
Batur	2014	1	60	--	NHL	C	None	--
Farah	2012	1	53	M	Angioimmunoblastic T-cell lymphoma	C	None	--
Shah	2011	1	88	M	MALT	C	--	--
Mani	2010	13	58 (mean)	M=10, F=3	DLBCL (n=3) EMZL (n=2) FL (n=2) BLL (n=2) Peripheral T-cell lymphoma, Primary effusion lymphoma, PBL, Mantle cell lymphoma (1 case each)	--	--	--
Mitropoulos	2000	1	26	F	T-cell lymphoblastic	C	Chemo	103m, A
Mcluggage	1996	1	75	F	MALT	C	Chemo	12m, U
Chatila	1996	1	45	M	LBL	C	None	18m, U
Friedman	1993	1	76	M	NHL, B-cell	C	Chemo + RT	Died postoperatively
Mosnier	1992	1	60	F	MALT	C	None	6m, A
Botha	1974	1	54	M	Lymphocytic lymphoma	C	--	15days, D
Vaittinen	1972	1	44	F	Lymphosarcoma	C	RT	3m, D
Vaittinen	1972	1	73	F	Lymphosarcoma	--	None	1.5m, D
Vaittinen	1972	1	75	F	Lymphocytic lymphoma	--	None	2m, D
Yasuma	1971	1	29	M	--	C	Chemo + RT	8m, D

PBL, plasmablastic lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; SLL, small lymphocytic lymphoma; MALT, mucosa associated lymphoid tissue; BLL, B-lymphoblastic lymphoma; LBL, large B-cell lymphoma. Surgery: C, cholecystectomy; Outcome: A, alive; D, dead; U, unknown.

gallbladder or marked irregular wall thickening, whereas, low-grade variants such as FL tend to produce slight thickening of the gallbladder wall (22, 23). Peri-portal lesions and para-aortic lesions are also commonly noted in these patients. In addition, CT or MRI findings of homogenous submucosal thickening of gallbladder wall with a preserved mucosal surface are also described as being suggestive of a lymphoma (21).

Currently, there are no guidelines for the management of gallbladder lymphomas. Single-case experiences report good long-term outcomes with cholecystectomy alone for lesions limited to the gallbladder (24, 25). There are very limited data on the role of adjuvant therapies in the treatment of gallbladder lymphoma (7, 17). In our series, we observed that patients who underwent resection demonstrated better outcomes compared to those who did not undergo surgical resection. In addition, patients who received adjuvant RT appeared to have superior long-term survival than those who underwent resection alone. However, due to the small number of patients in the comparison groups, we cannot derive any conclusions about the role of resection and adjuvant RT in this group of patients. In addition, most cases with gallbladder lymphomas are diagnosed on cholecystectomy specimens post-resection. Hence, identifying a role of adjuvant modalities post-resection is important for these cases.

We encountered certain limitations associated with using a population-based data registry including the retrospective nature of the study and limited information on some data points including clinical presentation, diagnostic modalities (radiology, CD markers), tumor size, grade, type of surgery (open *vs*. laparoscopic, simple *vs*. extended resections) and modified Ann Arbor staging for GI lymphomas. Moreover, since chemotherapy and immunotherapy data is not available in the SEER database, it is difficult to analyze their role in the long-term survival of these patients. Additionally, it could not be ascertained whether these cases were diagnosed incidentally or before surgery. Despite all these limiting factors, the most important benefit of this database is that we were able to analyze a large number of patients with such a rare disease, which is usually not possible through single-institution series. Using the information available in the SEER database, we are the first to report characteristics and survival outcomes of patients with PNHL-GB.

Conclusion

Primary gallbladder lymphomas are extremely rare. This study presents the largest series of PNHL-GB describing clinical features and outcomes of these patients in addition to summarizing the available literature. We observed significant differences in characteristics and survival outcomes amongst histological subtypes of PNHL-GB. Patients who had undergone surgical resection survived longer. In addition, adjuvant RT seems to provide some survival benefit. Further studies are needed to evaluate the role of adjuvant therapies particularly for patients with aggressive subtypes such as DLBCL.

Conflicts of Interest

All Authors declare that they have no conflict of interest and have no financial disclosures to report.

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The Authors AA, SR and AMAA and NSR participated in study conception and writing; EL and WR participated in data analysis and writing; FYB, GK and JM participated in study design, data interpretation and critical revision of the article.

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