Research Article

Clinicopathological Features, Treatment Strategy, and Prognosis of Primary Non-Hodgkin’s Lymphoma of the Duodenum: A SEER Database Analysis

Guoliang Zheng, Yue Wang, Yan Zhao, and Zhichao Zheng

Department of Gastric Surgery, Cancer Hospital of China Medical University (Liaoning Cancer Hospital and Institute), No. 44 Xiaoheyan Road, Dadong District, Shenyang, Liaoning 110042, China

Correspondence should be addressed to Zhichao Zheng; drzhengzhichao1@163.com

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Objective. Primary duodenal lymphoma (PDL) is extremely rare with limited data available in the literature. In this study, we sought to describe clinical features and identify factors affecting survival in patients with PDL using a large population cohort.

Methods. The Surveillance, Epidemiology, and End Results (SEER) database was queried from 1998 to 2015. Results. A total of 1060 cases of PDLs were identified. Clinicopathological features as well as survival data of PDLs were analyzed and compared with 10573 primary gastric lymphomas (PGLs) and 3239 primary small intestinal lymphomas (PSILs) from the SEER database. PDL patients were younger in age (60.96 ± 15.205), and the proportion of Ann Arbor stage I (53.21%) was higher. PDLs treated by surgery (8.68%) is the lowest among PDLs, PGLs, and PSILs. The 10-year survival rate of PDLs was significantly better than those of PGLs and PSILs, respectively (10-year survival rate: 21.24% vs. 20.40%, \(P = 0.027\); 10-year survival rate: 21.24% vs. 16.79%, \(P = 0.001\)). Age, gender, Ann Arbor staging, and histological type were regarded as independent prognostic factors for the difference in survival by multivariate analysis (all \(P < 0.05\)). Patients with <65 years, female, stage I, and FL were found to be significantly associated with good DSS. The treatment modality (surgery vs. conservative treatment) was not statistically related to DSS. The proportion of PDL patients who received surgical treatment gradually decreased from 15.60% in period 2 to 5.26% in period 4.

Conclusions. The clinicopathologic features of duodenal lymphoma were significantly different from those of gastric lymphoma and small intestinal lymphoma. The prognosis of PDLs was significantly better than those of the other two groups, and there was no statistical survival benefit from surgery in PDLs.

1. Introduction

The most predominant extranodal site in non-Hodgkin’s lymphoma (NHL) is the gastrointestinal (GI) tract [1], accounting for 5% to 20% of all NHL cases and 30% to 45% of all extranodal cases [2]. The lesion can occur in any part of the digestive tract from the mouth to the anus, of which stomach is the most common pathogenic sites (60%–75%) [3].

As primary duodenal lymphomas (PDLs) are exceedingly rare, the current researches about PDLs are based on anecdotal reports [4–23]. In the present study, we retrospectively reviewed the clinical and pathological manifestations of lymphomas of duodenal lymphoma for cases based on the largest sample size so far to identify prognostic factors and to clarify the value of treatment modalities in the management of these malignancies.

2. Materials and Methods

2.1. Data Source and Patient Selection. We queried the SEER database (SEER, 18 November 2017) with SEER Stat version 8.3.5 software to identify 14872 patients who were diagnosed with lymphoma from 1998 to 2015, including 1060 PDLs, 10573 primary gastric lymphomas (PGLs), and 3239 primary small intestinal lymphomas (PSILs). The codes used for
lymphoma in the coding system of the International Classification of Diseases for Oncology (ICD-O)-3 were 9590–9729. The search was limited to adult patients (≥18 years old) with the type of follow-up equal to "active follow-up." The exclusion criteria were as follows: (i) patients without definitely histological confirmation; (ii) patients with only autopsy or death certificate records; (iii) patients with incomplete survival data and follow-up information; (iv) patients without Ann Arbor stage record; and (v) patients without the information of surgery. After screening, we got a total of 10321 patients.

Clinical and pathological variables (e.g., age, gender, race, sex, age at diagnosis, marital status, year of diagnosis, histological type, Ann Arbor stage, whole body symptom of lymphoma based on the AJCC (6th edition) staging system, treatment modalities employed and information of “cause of death and follow-up,” and “multiple primary field”) were extracted from the SEER.

Since the SEER cause-specific death classification variable is defined by taking into account cause of death in conjunction with sequence of tumor occurrence (i.e., only one tumor or the first of multiple tumors) and comorbidities (e.g., AIDS and/or site-related diseases), we excluded the patients except that lymphoma was the only one primary cancer or the 1st cancer of 2 or more primaries to avoid the ambiguity of the lymphoma-specific survival [24].

The survival data were available in the measurement unit of months, without precise days. Considering the preconditions that no precise survival days were available and that patients with only autopsy or death certificate records were excluded, a survival time of 0 months was recorded as 0.5 months to include patients who died within 1 month of diagnosis but who did not reach the 1-month threshold [25, 26].

Since this study only involves analysis of the publically available database (SEER) and does not contain any identifying patient information, the ethical approval of this study by the institutional review board (IRB) is not required.

### 2.2. Statistical Analyses

Statistical analyses were performed using the statistical software SPSS 22.0 for Apple (SPSS Inc., Chicago, IL). Numerical variables were expressed as mean ± SD and were analyzed by the t-test. Discrete variables were analyzed using the chi-square test or Fisher’s exact test. Risk factors for survival were identified by univariate analysis, and COX regression was employed for multivariate analysis. Disease-specific survival (DSS) was analyzed by the Kaplan–Meier method and differences between the curves were compared using the log-rank test. All P values were two-sided, and P values < 0.05 were considered statistically significant.

### 3. Results

#### 3.1. Baseline Demographic Characteristics

Clinical and pathological features of primary duodenum lymphoma (PDL) are summarized in Table 1. In total, 1060 eligible PDL patients were recognized during the 18-year study period (between 1998 and 2015). There was no obvious sex trend:

| Clinicopathologic features | Number of assessable patients (%) |
|-----------------------------|----------------------------------|
| **Age (years)**             |                                 |
| Mean ± SD                   | 60.96 ± 15.205                   |
| ≥60                         | 578 (54.53)                      |
| <60                         | 482 (45.47)                      |
| **Gender**                  |                                 |
| Male                        | 604 (56.98)                      |
| Female                      | 456 (43.02)                      |
| **Marital status**          |                                 |
| Married                     | 611 (57.65)                      |
| Unmarried                   | 349 (32.92)                      |
| Unknown                     | 100 (9.43)                       |
| **Race**                    |                                 |
| White                       | 878 (82.83)                      |
| Black                       | 69 (6.51)                        |
| Others                      | 93 (8.77)                        |
| Unknown                     | 20 (1.89)                        |
| **Ann Arbor staging**       |                                 |
| I                           | 564 (53.21)                      |
| II                          | 182 (17.17)                      |
| III                         | 40 (3.77)                        |
| IV                          | 173 (16.32)                      |
| Unknown                     | 101 (9.53)                       |
| **Symptoms**                |                                 |
| A                           | 463 (43.68)                      |
| B                           | 127 (11.98)                      |
| Unknown                     | 470 (44.34)                      |
| **Histological type**       |                                 |
| DBCLC                       | 348 (32.83)                      |
| MALT                        | 146 (13.77)                      |
| T-cell                      | 28 (2.64)                        |
| FL                          | 436 (41.13)                      |
| MCL                         | 29 (2.74)                        |
| Unknown                     | 73 (6.89)                        |
| **Combined with other cancers** |                                 |
| Yes                         | 111 (10.47)                      |
| No                          | 949 (89.53)                      |
| **Treatment modality**      |                                 |
| Only surgery                | 41 (3.87)                        |
| Surgery + conservative      | 51 (4.81)                        |
| Conservative                | 968 (91.32)                      |

DLBCL = diffuse large B-cell lymphoma; ETCL = T-cell lymphoma; FL = follicular lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma.

604 were male and 456 were female. Age was from 7 to 99 years (median, 62 years; mean, 60.96 ± 15.205 years). Most patients were married (611; 57.65%) and white (878; 82.83%). 55.66% of the patients had clear symptoms, of which the symptoms of A were 463 (43.68%) and B were 127 (11.98%). Out of 1060 PDL specimens, follicular lymphoma (FL) was observed in 436 (41.13%) of them, and diffuse large B-cell lymphoma (DLBCL) in 348 of the tumor specimens (32.83%) was observed. The majority of patients (949, 89.85%) had single tumor, and only 111 (10.47%) patients had multiple tumors. Among 1060 patients, 92 underwent surgery alone or associated with conservative treatment (chemotherapy alone, radiotherapy alone, chemotherapy + radiotherapy, or Helicobacter pylori infection).
eradication only), and the other 968 received conservative treatment.

Next, clinical and pathological features of 1060 PDLs were compared with those of 10573 PGLs and 3239 PSILs (Table 2). The results showed that there were no significant differences in age, gender, marital status, race, and other cancers between the surgery and conservative groups. However, primary site, Ann Arbor staging, symptoms, and histological type were significantly different between the two groups (all $P < 0.05$); that is, incidence of cancers with I stage or A symptoms was significantly higher in the conservative group compared to that in the surgery group.

The results showed that age, gender, symptom, and histological type were significantly different between PDLs and PGLs (all $P < 0.05$); that is, incidence of tumors with younger patients or more follicular lymphoma was significantly higher in the PDL group compared to that in the PGL group. The PDL group also showed younger patients, earlier Ann Arbor staging, more follicular lymphoma, and more surgery treatment in comparison with those of the PSIL group (all $P < 0.05$).

### Table 2: Comparison of clinicopathological parameters among PDLs, PGLs, and PSILs.

| Clinicopathologic features | PDLs ($n = 1060$) | PGLs ($n = 10573$) | $P$ value | PSILs ($n = 3239$) | $P$ value |
|----------------------------|-------------------|-------------------|----------|-------------------|----------|
| **Age (years)**            |                   |                   |          |                   |          |
| Mean ± SD                  | 60.96 ± 15.205    | 66.08 ± 14.957    | $< 0.001$| 62.41 ± 16.779    | 0.013    |
| ≥60                        | 578 (54.53)       | 7205 (68.15)      | $< 0.001$| 1927 (59.49)      | 0.004    |
| <60                        | 482 (45.47)       | 3368 (31.85)      |          | 1312 (40.51)      |          |
| **Gender**                 |                   |                   |          |                   |          |
| Male                       | 604 (56.98)       | 5617 (53.13)      |          | 1931 (59.62)      |          |
| Female                     | 456 (43.02)       | 4956 (46.87)      |          | 1308 (40.38)      |          |
| **Ann Arbor staging**      |                   |                   |          |                   |          |
| I                          | 564 (53.21)       | 5616 (53.12)      |          | 1239 (38.25)      |          |
| II                         | 182 (17.17)       | 1541 (14.58)      |          | 1047 (32.32)      |          |
| III                        | 40 (3.77)         | 482 (4.56)        |          | 143 (4.41)        |          |
| IV                         | 173 (16.32)       | 1731 (16.37)      |          | 567 (17.52)       |          |
| Unknown                    | 101 (9.53)        | 1203 (11.37)      |          | 243 (7.50)        |          |
| **Symptoms**               |                   |                   |          |                   |          |
| A                          | 463 (43.68)       | 3260 (30.83)      | $< 0.001$| 1174 (36.25)      |          |
| B                          | 127 (11.98)       | 1313 (12.42)      |          | 432 (13.33)       |          |
| Unknown                    | 470 (44.34)       | 6000 (56.75)      |          | 1633 (50.42)      |          |
| **Histological type**      |                   |                   |          |                   |          |
| DLBCL                      | 348 (32.83)       | 5168 (48.88)      | $< 0.001$| 1778 (54.89)      |          |
| MALT                       | 146 (13.77)       | 4323 (40.89)      |          | 265 (8.18)        |          |
| T-cell                     | 28 (2.64)         | 78 (0.74)         |          | 185 (5.71)        |          |
| FL                         | 436 (41.13)       | 236 (2.23)        |          | 744 (22.97)       |          |
| MCL                        | 29 (2.74)         | 131 (1.24)        |          | 51 (1.57)         |          |
| Unknown                    | 73 (6.89)         | 637 (6.02)        |          | 216 (6.68)        |          |
| **Treatment modality**     |                   |                   |          |                   |          |
| Only surgery               | 41 (3.87)         | 401 (3.79)        |          | 928 (28.65)       |          |
| Surgery + conservative     | 51 (4.81)         | 619 (5.85)        |          | 1173 (36.22)      |          |
| Conservative               | 968 (91.32)       | 9553 (90.36)      |          | 1138 (35.13)      |          |

DLBCL = diffuse large B-cell lymphoma; ETCL = T-cell lymphoma; FL = follicular lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma.

3.2. Survival and Prognostic Factors. In order to analyze the prognosis among duodenum, gastric, and small intestinal lymphomas, survivals of 1060 PDLs were compared to those of 10573 PGLs and 3239 PSILs (Figure 1). The results showed that the DSS of PDLs were significantly better than those of PGLs and PSILs (10-year survival rate: 21.24% vs. 20.40%, $P = 0.027$; 10-year survival rate: 21.24% vs. 16.79%, $P = 0.001$).

Furthermore, univariate and multivariate analyses were performed to evaluate the prognosis of PDLs (Table 3). Age, gender, Ann Arbor staging, and histological type were regarded as independent prognostic factors for the DSS (all $P < 0.05$). Symptom was regarded as a significant risk factor for the DSS by univariate analysis ($P = 0.002$), while it is not an independent prognostic factor for DSS by multivariate analysis.

3.3. Stratified Analysis. We showed stratified analysis according to several prognostic variables based on multivariate analyses (Figure 2). Patients with <65 years, female, stage I, and FL were found to be significantly associated with good DSS. However, patients with ≥60 years, male, stage IV, and TCL were found to be significantly associated with poor DSS (all $P < 0.05$).

Figure 3 shows the changing trend of treatment modalities to PGL. The changing trends of treatment modalities to PDL were analyzed in 4 consecutive time periods: from 1998 to 2000 (period 1), from 2001 to 2005 (period 2), from 2006 to 2010 (period 3), and from 2011 to 2015 (period 4).
proportion of patients who received conservative treatment increased from 84.40% in period 2 to 94.74% in period 4, whereas patients who received surgical treatment gradually decreased from 15.60% in period 2 to 5.26% in period 4.

4. Discussion

To the best of our knowledge, the current study represented the largest number of PDLs. In this study, we summarized clinical and pathological features of 1060 cases of PDLs. We further analyzed prognosis of PDLs in comparison with that of PGLs and PSILs. It was found that tumors with younger patients or more follicular lymphoma was significantly higher in PDLs. In addition, PDLs had poorer prognosis compared to PGLs and PSILs. These observations indicate that surgery treatment may not play a role in improving survival in patients as compared to conservative treatment. Since 2000, the proportion of PDL patients undergoing surgery has declined.

We know that follicular lymphoma (FL) is primarily a nodal disease and primary FL of the gastrointestinal (GI) tract is rare [27]. However, the most common histological subtype is FL, followed by DLBCL among of PDLs [22]. Our study showed that the proportion of FL was the highest (44.13%) and significantly higher than that of stomach (22.3%) and small intestine (22.97%). Therefore, the predominance of the follicular histology in PDL was interesting. The high proportion of follicular lymphoma in duodenal lymphoma might be an important reason why the prognosis was better than that of the stomach and small intestine.

Table 3: Univariate and multivariate analysis for DSS in the PGLs.

| Characteristics                  | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | HR                  | 95% CI                | P value | HR                  | 95% CI                | P value |
| Age (years)                      | 1.026               | 1.017–1.035           | <0.001  | 1.027               | 1.018–1.036           | <0.001  |
| Gender                           | 0.636               | 0.491–0.824           | 0.001   | 0.633               | 0.487–0.823           | 0.001   |
| Marital status                   | 1.136               | 0.950–1.358           | 0.162   |                     |                      |         |
| Symptom                          | 1.239               | 1.083–1.417           | 0.002   |                     |                      |         |
| Ann Arbor staging                | 1.189               | 1.099–1.286           | <0.001  | 1.202               | 1.107–1.306           | <0.001  |
| Histological type                | 0.696               | 0.638–0.759           | <0.001  | 0.718               | 0.656–0.786           | <0.001  |
| Combined with other cancers      | 0.724               | 0.483–1.087           | 0.119   |                     |                      |         |
| Treatment modality               | 1.158               | 0.993–1.349           | 0.061   | 1.034               | 0.906–1.182           | 0.618   |

Figure 1: Comparison of DSS among PDLs, PGLs, and PSILs. The results showed that the DSS of PDLs were significantly better than those of PGLs and PSILs (10-year survival rate: 21.24% vs. 20.40%, \( P = 0.027 \); 10-year survival rate: 21.24% vs. 16.79%, \( P = 0.001 \)). PDLs vs. PGLs: \( P < 0.05 \); PDLs vs. PSILs: \( P < 0.05 \). PGL, primary gastric lymphoma; PSIL, primary small intestinal lymphoma; PDL, primary duodenum lymphoma.
Our study showed that the mean age (60.96 ± 15.205) of patients with PDL was younger than that of the stomach and small intestine, and that the proportion of stage I was also higher than that of the stomach and small intestine. Pfl he duodenal anatomy site is special, the tumor growth space is small, and the patient presents the discomfort symptom earlier than the stomach and small intestine. At the same time, EUS can not only clarify the lesions on the mucosal surface of the gastrointestinal tract but also understand the changes in the hierarchical structure of the gastrointestinal

Figure 2: The stratified analysis according to (a) age, (b) gender, (c) Ann Arbor staging, and (d) histological type in the PDLs. Patients with <65 years, female, stage I, and FL were found to be significantly associated with good DSS. However, patients with ≥60 years, male, stage IV, and TCL were found to be significantly associated with poor DSS (all P < 0.05).
may be associated with a high risk of life-threatening complications [28]. Surgery is also required for removal of residual disease after medical debulking [32]. Since the SEER database does not list the complications, this paper cannot discuss the complications.

Although there was no statistically significant difference in survival by treatment modalities in the multivariate analysis, there are other multiple factors that contribute to survival. In previous studies, female, low-grade histology and good PS have been reported to be associated with high OS. However, age >60 years, advanced stage, poor performance status (PS), and elevated lactic dehydrogenase (LDH) were associated with poor outcome [3, 32–34]. In our study, age, gender, Ann Arbor staging, and histological type retained independent prognostic factors in the multivariate analysis. Patients with <65 years, female, stage I, and FL were found to be significantly associated with good DSS. LDH and PS are not mentioned in the SEER database, so statistical analysis cannot be made in this paper.

Although it is an excellent resource for comparative outcome analysis for all malignancies involving the gastrointestinal tract, SEER has its limitations. Since the database provides passive follow-up for its registered cases, incomplete data reporting remains a problem. First, much information could not be obtained from the SEER database, such as PS and LDH. Second, the SEER database also did not describe postoperative complications and quality of life score, so we were unable to assess the complications and quality of life associated with surgery.

**Abbreviations**

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone
COPD: chronic obstructive pulmonary disease
CVP: cyclophosphamide, vincristine, and prednisone
died
DLBCL: diffuse large B-cell lymphoma
DSS: disease-specific survival
ETCL: enteropathy-type T-cell lymphoma
F: female
FL: follicular lymphoma
JGCA: Japanese Gastric Cancer Association
L: live
LDH: lactic dehydrogenase
M: male
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
NHL: non-Hodgkin’s lymphoma
NR: no recurrence
PDL: primary duodenum lymphoma
PGIL: primary gastrointestinal
PGLs: primary gastric lymphoma
PS: performance status
PSILs: primary small intestinal lymphoma
R: recurrence
R- rituximab with CHOP
CHOP:
SEER: Surveillance, Epidemiology, and End Results
Data Availability
No additional data are available.

Conflicts of Interest
The authors declare that they have no conflicts of interest to this work.

Authors’ Contributions
ZGL conceived the study and drafted the manuscript. WY and ZY participated in drafting the manuscript. ZZC designed and supervised the study. All authors contributed to the writing of the manuscript and provided final approval of the manuscript. All authors have read and approved the final version of this manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 4: Previously reported cases of PDLs.

| Reference       | Num | Age | Sex | Location         | Type          | Stage | CD markers                  | Surgery       | Conservation | Follow-up |
|-----------------|-----|-----|-----|------------------|---------------|-------|----------------------------|---------------|--------------|-----------|
| Zheng et al.    | 1   | 58  | M   | ——               | MCL           | III   | CD20, CD21, CD5, BCL-2     | None          | None         |           |
| Linnik et al.   | 1   | 51  | M   | ——               | DLBCL         | III   | CD20, CD45, BCL2, BCL6     | None          | Chemotherapy | 60 mo/L  |
| Iwamuro et al.  | 2   | 52  | M   | Descendant duodenum | FL           | IV    | CD20, CD10, BCL2           | None          | R           |           |
| Iwamuro et al.  | 1   | 56  | M   | Papilla          | FL            | IV    | CD20, CD10, BCL2           | None          | Bendamustine and R |           |
| Mejia et al.    | 1   | 60  | M   | Descendant duodenum | FL            | IV    | CD20, CD10, BCL2           | None          | R           |           |
| Linnik et al.   | 1   | 51  | M   | Descendant duodenum | FL            | IV    | CD20, CD10, BCL2           | None          | R           |           |
| Iwamuro et al.  | 1   | 56  | M   | Papilla          | FL            | IV    | CD20, CD10, BCL2           | None          | R           |           |
| Tari et al.     | 1   | 66  | F   | Ampulla of Vater | DLBCL         | III   | CD20, CD10, BCL-2          | Chemotherapy  | 2 y/L        |           |
| Du et al.       | 1   | 65  | M   | Ampulla of Vater | DLBCL         | I     | CD20, CD10, BCL-2          | None          | None         |           |
| Cho et al.      | 1   | 68  | M   | Ampulla of Vater | MALT          |       | CD20, CD10, BCL2           | R-CHOP        | 30 mo/R      |           |
| Kondo et al.    | 1   | 78  | F   | Ampulla of Vater | DLBCL         | I     | CD20, CD10, BCL-2          | R-CHOP        | 19 mo/NR     |           |
| Nakase et al.   | 1   | 57  | F   | Papilla          | FL            | I     | CD10, Bcl-2                | None          | None         | 1 mo/NR    |
| Born et al.     | 1   | 75  | M   | ——               | FL            |       | ——                         | None          | None         |           |
| Woo et al.      | 1   | 71  | F   | Descendant duodenum | MALT          | III2  | CD20                       | None          | CVP          | 1 y/NR     |
| Chim et al.     | 1   | 73  | M   | Ampulla of Vater | DLBCL         | I     | CD20, BCL-6                | None          | CHOP         | Died due to COPD |
| Jabr [18]       | 1   | 71  | F   | Ampulla of Vater | DLBCL         | III   | CD20, CD10, CD45, BCL-2    | None          | Chemotherapy |           |
| Zenda et al.    | 1   | 49  | F   | Papilla          | FL            | I     | CD20, CD10, CD45, BCL-2    | None          | R-CHOP       |           |
| Yildirim et al. | 1   | 33  | M   | Ampulla of Vater | DLBCL         | III   | CD20                       | None          | CHOP         | 1 y/NR     |
| Nadal et al.    | 1   | 46  | M   | Ampulla of Vater | MALT          | III   | BCL-2                      | None          | Radiation    | 4 y/NR     |
| Ventrucci et al.| 1   | 55  | M   | Ampulla of Vater | FL            | I     | CD10, Bcl-2                | None          | CHOP         | 2 y/NR     |
| Ventrucci et al.| 1   | 65  | F   | Ampulla of Vater | MALT          | III   | CD20, CD79a, BCL-2         | None          | CVP          | 15 mo/NR   |
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