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The role of surgical management in primary small bowel lymphoma: A single-center experience

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Abstract

Introduction: Information on primary small intestinal lymphoma is more limited than for gastric lymphoma because most of the previous studies did not focus on the former. Few prognostic indicators in primary intestinal lymphoma have been reliably established because of limited patient numbers and variations in criteria for patient selection. In this study, we retrospectively reviewed the clinical and pathological characteristics of small intestinal lymphoma cases from our hospital, to determine prognostic factors and to clarify the effect of surgical resection on prognosis.

Methods: Eighty-two patients were enrolled in this retrospective study between January 1997 and December 2012. Patients were divided into two groups based on whether or not they underwent surgical management. Gross resection was defined as complete removal of the primary lesion(s), as confirmed by the naked eye. Combined therapy refers to concurrent surgery and chemotherapy. The clinicopathological characteristics and long-term outcomes of patients were analyzed and compared between the two groups.

Results: Most of the patients had abdominal pain (75.6%), and some had loss of body weight (29.3%) and bowel perforation (22.0%). Sixty-two patients (75.6%) underwent surgical management. Patients in the surgery group presented with fewer B symptoms (fever, night sweats, and weight loss; $P = 0.035$) but more bulky disease ($P = 0.009$). The ileocecal region was the most common site of solitary involvement (34.1%). The most common reason for surgery was for tumor-related complications (61.3%). Seven patients (11.3%) developed major complications of surgery, but these were not related to the indication, timing, or type of surgery. Only major surgical complications were statistically significant in relation to early mortality ($P = 0.004$). The estimated 5-year progression-free survival (PFS) was 35.1% and 5-year overall survival (OS) was 43.2%. Univariate analysis revealed that patients in the surgery group had improved 5-year PFS ($P = 0.028$). T-cell lymphoma, involvement of multiple gastrointestinal regions and extranodal involvement, higher scores for International Prognostic Index (IPI), more advanced Ann Arbor stage, lactate dehydrogenase (LDH) levels above 215 U/L, and management without combined therapy were prognostic for shorter PFS and OS in univariate analyses. Individuals who received R0 resection or gross resection had improved 5-year PFS and OS. Cox regression analysis demonstrated that primary T-cell lymphoma was an independent negative prognostic factor for both OS and PFS.

Conclusion: Combined therapy is an independent prognostic factor for long-term survival in small intestinal lymphoma. Gross resection is recommended in patients with small intestinal lymphoma and leads to improved PFS without significantly increasing the risk of complications. Emergency surgery does not lead to poor prognosis. However, caution is warranted in the management of all patients, because of the high risk of post-operative complications and potential for early mortality.

Keywords: Small intestinal lymphoma; Surgery; Combined therapy; Emergency operation; Prognosis

Introduction

The most frequent extranodal site in non-Hodgkin lymphoma (NHL) is the gastrointestinal (GI) tract,[1,2] which accounts for 5–20% of all extranodal NHLs and 2% of small intestinal malignancies.[3] Approximately 60–75% of

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primary GI lymphomas are located in the stomach, and involvement of other parts of the GI tract is considerably less common.[1,2,4,5] There is less information on primary intestinal NHL because most previous studies focused on gastric lymphoma.[1,6,7] Although a few prognostic factors concerning primary intestinal lymphoma – including biochemical abnormalities, patient status, histologic subtype, and clinical stage – have been proposed, the relevance of these factors for optimizing treatment remains unclear due to low patient numbers and variation in criteria used for patient selection.[8–11] Traditionally, chemotherapy has been important for management of GI lymphoma, with surgical resection being recommended only under specific circumstances. However, many authors have advocated a combination of surgery and chemotherapy to improve overall survival.[8,9,11–13] In the previous studies, cancers of each of the various regions of the GI tract were included, and lymphomas of the small intestine lymphoma were rarely discussed separately. In the present study, we retrospectively reviewed the clinical and pathological manifestations of lymphomas of the small intestine for cases from our hospital, to identify prognostic factors and to clarify the value of surgical resection in the management of these malignancies.

Materials and methods

Patient population

One-hundred-and-seventy-eight patients with intestinal lymphoma were reviewed. After exclusion of minors, patients with a solitary large intestinal lymphoma, or who did not undergo treatment, a total of 82 patients were enrolled in this retrospective study at Chang Gung Memorial Hospital Linkou Medical Center (Taoyuan, Taiwan) between January 1997 and December 2012, with a follow-up period ranging from 0.1 months to 232.9 months (mean ± standard error of the mean (SEM): 47.0 ± 6.6 months). Patients were divided into two groups based on whether or not they underwent surgical management. Surgical management included R0 resection (no microscopically visible malignant cells at the resection margin), R1 resection (malignant cells microscopically visible only), and limited procedure (partial resection or open biopsy). Gross resection was defined as complete removal of the primary lesion(s) confirmed by the naked eye; thus, R0 and R1 resection were both included. A combined therapy meant both concurrent surgery and chemotherapy. With the approval of the Institutional Review Board, the clinicopathological characteristics and long-term outcomes of patients were analyzed and compared between the two groups.

Data collection and statistical analysis

Information on demographics, characteristics of the primary tumor, surgical details, and the course of hospitalization was collected from medical records. Tumor complications included bowel obstruction, any sign of GI hemorrhage, or bowel perforation. Patients with persistent post-operative intra-abdominal infection, evidence of leakage from anastomosis, prolonged sepsis, or ileus necessitating reoperation, were considered to have a major surgical complication. Patients who died within 30 days after diagnosis of lymphoma ($n = 7$) were categorized as having experienced early mortality and were considered separately. The seven patients within this category were excluded from the survival analysis to avoid any confounding effect of pre-existing disease on the exposure–mortality relationship.[14] The Ann Arbor staging system was used for clinical staging,[15] and the International Prognostic Index (IPI)[16] was also calculated and compared.

Statistical analyses were performed using the statistical software SPSS 20.0 (IBM Corp., Armonk, NY, USA). Outcome measures included progression-free survival (PFS) and overall survival (OS) after diagnosis. Fisher's exact test was used to compare clinicopathologic features. Continuous data are presented as the mean ± SEM, and were analyzed by the *t*-test. PFS and OS were estimated using the Kaplan–Meier method, and any significant difference between the subgroups (detected by univariate analysis) was compared using the log-rank test. Multivariate analysis was conducted using the Cox regression model (backward stepwise method). *P* values <0.05 were considered statistically significant.

Ethics statement

This retrospective analysis was approved by the Chang Gung Medical Foundation Institutional Review Board (102-0678B). The Chang Gung Medical Foundation Institutional Review Board judged that written informed consent of the patients or their family was not necessary for this kind of retrospective study.

Results

Demographic characteristics

Fifty-two of 82 patients (63.4%) were followed for more than 6 months after diagnosis. Most of the patients had abdominal pain (75.6%), while others had loss of body weight (29.3%) and bowel perforation (22.0%); hemorrhage of the GI tract and obstruction were less common (both 18.3%). Obstructive jaundice was rare but occurred in three patients in our series. Sixty-two patients (75.6%) underwent surgical management. Demographic data are summarized in Table 1. There were no significant differences in gender and age between the surgery and non-surgery groups. Patients in the surgery group showed fewer B symptoms (fever, night sweats, and weight loss; 11.3% vs. 35.0%; $P = 0.035$) but more bulky disease (>10 cm in diameter; 35.1% vs. 5.0%; $P = 0.009$). Among the 82 patients, multiple site involvement of lymphoma was most frequent (37.8%), but the ileocecal region was the

Table 1
Patient demographics and characteristics of primary malignancy.

	Surgery (n = 62)	No surgery (n = 20)	*P* value
Gender			
Male	46 (74.2%)	14 (70.0%)	0.774
Female	16 (25.8%)	6 (30.0%)	
Age (years)			
Mean ± SEM	60.7 ± 2.0 (23–90)	67.4 ± 2.8 (38–91)	0.082
Median	62.5	69.0	
≥65	30 (48.4%)	11 (55.0%)	0.798
Follow-up period (months)			
Mean ± SEM	54.4 ± 8.2 (0.1–232.9)	23.9 ± 7.3 (0.6–135.9)	0.007
B Symptom	7 (11.3%)	7 (35.0%)	0.035
Bulky disease	20 (35.1%, n=57)	1 (5.0%)	0.009
GI location			
Duodenum	0 (0.0%)	2 (10.0%)	0.082[a]
Jejunum and ileum	18 (29.0%)	3 (15.0%)	
Ileocecal area	22 (35.5%)	6 (30.0%)	
Multiple regions	22 (35.5%)	9 (45.0%)	
β2-microglobulin (μg/L)			
Mean ± SEM	2384.5 ± 166.6 (899–7469)	2739.1 ± 266.9 (1565–5149)	0.273
Median	2051.2	2415.4	
>3000	9 (18.0%, n=50)	7 (38.9%, n=18)	0.105
LDH (U/L)			
Mean ± SEM	212.8 ± 56.2 (28–2754)	327.4 ± 102.8 (17–1800)	0.305
Median	111.5	178.0	
>215	14 (28.0%, n=50)	8 (42.1%, n=19)	0.386
Extranodal involvement			
Single	38 (61.3%)	8 (40.0%)	0.122
Multiple	24 (38.7%)	12 (60.0%)	
IPI			
0 or 1	28 (45.2%)	6 (30.0%)	0.300
2 or more	34 (54.8%)	14 (70.0%)	
Ann Arbor staging			
Stage I or II	40 (64.5%)	7 (35.0%)	0.036
Stage III or IV	22 (35.5%)	13 (65.0%)	
Immunophenotype			
B-cell	47 (75.8%)	20 (100.0%)	0.017
T-cell	15 (24.2%)	0 (0.0%)	

GI: gastrointestinal; IPI: International Prognostic Index; LDH: lactate dehydrogenase; SEM: standard error of the mean.
[a] Estimation with Monte Carlo simulation.

most common site in solitary lymphomas (34.1% of patients). There was no significant difference between the two groups in lactate dehydrogenase (LDH) levels, β2-microglobulin levels, extranodal involvement, and International Prognostic Index (IPI) score. Compared with patients who underwent surgery, those who had not undergone surgery had a higher incidence of advanced stage lymphoma (65.0% vs. 35.5%; $P = 0.036$) and were more frequently with the immunophenotype of B-cell (100.0% vs. 75.8%; $P = 0.017$).

Surgical management and results

Among the reasons for initiating surgical management, 61.3% were for tumor-related complications. Bowel perforation were the most common (18/38, 47.4%), followed by intestinal obstruction (36.8%). Fifty-two of the 62 patients underwent gross resection (83.9%) and 42 achieved R0 resection (67.7%). Seven patients (11.3%) developed major surgical complications that were deemed not related to the indication for surgery, timing, or type of surgery. There were eight patients with early mortality, and seven of these occurred in the surgery group (11.3% vs. 5.0%; $P = 0.672$). Patients developed major surgical complications were statistically significant in relation to early mortality ($P = 0.004$) (Table 2).

Progression-free survival and overall survival

For all patients included in this study (excluding those with early mortality, n = 74), the median time to progression was 13.3 months and the median survival time was 25.9 months. The estimated 5-year PFS was 35.1% and the 5-year OS was 43.2%. Univariate analysis of prognostic factors revealed that the patients in the surgery group had better 5-year PFS ($P = 0.028$), but there was no significant difference for OS ($P = 0.067$). T-cell lymphoma, multiple GI region and extranodal involvement, higher IPI score,

Table 2
Management, complications, and prognosis.

	Surgery (n = 62)		No surgery (n = 20)	*P* value
	With C/T (n = 48)	Without C/T (n = 14)		
Surgical indications				
Mass resection	21 (43.8%)	3 (21.4%)		
Tumor complications	27 (56.2%)	11 (78.6%)		
Obstruction	10 (37.0%)	4 (36.4%)		
Bleeding	4 (14.8%)	2 (18.2%)		
Perforation[a]	13 (48.2%)	5 (45.4%)		
Resection status				
R0 resection	36 (75.0%)	6 (42.9%)		
Gross resection (R0 + R1)	43 (89.6%)	9 (64.3%)		
Major surgical complication	7 (11.3%)			
Emergency operation	3/18			0.404
Operation for tumor complications	6/38			0.232
R0 resection	4/42			0.671
Gross resection	4/52			0.076
Early mortality	7 (11.3%)		1 (5.0%)	0.672
Major surgical complication	3/7		–	0.026
Emergency operation	3/18		–	0.404
Operation for tumor complications	6/38		–	0.232
R0 resection	3/42			0.199
Gross resection	5/52			0.314
Overall survival (month)	n=55		n=19	
Mean ± SEM	70.4 ± 9.5 (1.1–237.1)		33.9 ± 11.5 (1.4–194.3)	0.018
Median	58.7		8.5	
Progression free survival				
Mean ± SEM	59.9 ± 9.3 (0.8–237.1)		19.9 ± 7.2 (1.4–124.0)	0.001
Median	21.1		7.0	

C/T: chemotherapy; SEM: standard error of the mean.
[a] All patients with perforations underwent emergency operation.

advanced Ann Arbor stage, LDH level above 215 U/L, and management without combination of surgery and chemotherapy were prognostic for shorter PFS and OS in univariate analyses. In contrast, age less than 65 years and management with chemotherapy were significant prognostic factors for longer OS (Table 3). Patients who received R0 resection or gross resection had both better 5-year PFS and OS (Fig. 1).

Cox regression analysis demonstrated primary T-cell lymphoma as an independent negative prognostic factor for OS. In addition, treatment without gross resection was associated with worse PFS, and treatment without combined therapy was associated with worse OS (Table 4). Estimated PFS and OS curves based on the major independent prognostic factors are shown in Fig. 2.

Discussion

GI malignancy in the stomach or large intestine can be diagnosed easily by endoscopy. In contrast, small intestinal lesions are difficult to manage, and specialized instruments – such as the capsule endoscope – despite their indispensability for diagnosis, are not always available.[17–20] Thus, surgery may represent the main diagnostic technique in small bowel lesions or neoplasms. Combined therapy with surgery and chemotherapy for primary GI lymphoma can extend long-term survival and has been recommended in most reports. However, chemotherapy is considered to be the most important treatment strategy on the premise that lymphoma is a systemic disease. In gastric and colon lymphoma, some authors have proposed that surgical resection should be delayed until the occurrence of tumor-related complications.[5,21–24] Moreover, radical surgery may lead to other complications, resulting in a need to postpone chemotherapy. These opinions were proposed based on information on primary gastric lymphoma or combined data from all GI tract lymphomas; the optimal management of lymphoma of the small intestine has seldom received separate consideration. In the present study, we observed that PFS and OS were significantly improved in the surgery group compared with the non-surgery group. Univariate analysis revealed longer 5-year PFS in the surgery group, and longer 5-year OS in those receiving chemotherapy. In addition, significant improvements were found in 5-year PFS and OS in patients who achieved R0 resection, and we also obtained the same result for gross resection. Based on univariate and multivariate analyses, combined therapy with surgery and chemotherapy was an independent positive prognostic factor for 5-year OS. Besides, we also found about 40% of patients died and half of patients suffered from disease progression within one year. Most of them died from tumor progression and chemotherapy-related complications. Nevertheless,

Table 3
Progression-free and overall survival in relation to patient characteristics, disease indicators and treatment modality.

	No. of patients	5-year progression-free survival (%)	*P* value	5-year overall survival (%)	*P* value
Overall	74	35.1%		43.2%	
Age (years)					
<65	36	44.4%	0.159	52.8%	0.043
≥65	38	26.3%		34.2%	
Gender					
Male	56	33.9%	0.663	41.1%	0.410
Female	18	38.9%		50.0%	
Immunophenotype					
B-cell	63	41.2%	0.002	49.1%	0.002
T-cell	11	0.0%		9.1%	
GI location					
Single region of small intestine	46	47.7%	0.001	49.8%	0.029
Multiple regions	28	14.3%		32.1%	
B symptom					
No	61	39.3%	0.153	47.5%	0.460
Yes	13	15.4%		23.1%	
Extranodal involvement					
Single	43	55.7%	0.000	60.4%	0.000
Multiple	31	6.5%		19.4%	
IPI					
0 or 1	33	60.5%	0.000	72.6%	0.000
≥ 2	41	14.6%		19.5%	
Ann Arbor stage					
I or II	45	53.2%	0.000	62.1%	0.000
III or IV	29	6.9%		13.8%	
Bulky disease (n = 69)					
No	50	35.9%	0.308	41.8%	0.397
Yes	19	26.3%		36.8%	
β2-microglobulin level (n = 65)					
≤3000	52	46.1%	0.011	53.7%	0.088
>3000	13	15.4%		30.8%	
LDH level (n = 64)					
≤215	46	43.4%	0.022	56.4%	0.012
>215	18	22.2%		22.2%	
Treatment modality			0.010		0.012
Surgery alone	8	25.0%	0.028 (surgery vs. combination)	25.0%	0.010 (surgery vs. combination)
Combination of surgery and C/T	47	44.7%	0.007 (combination vs. C/T)	55.3%	0.022 (combination vs. C/T)
C/T alone	19	15.8%	0.543 (C/T vs. surgery)	19.7%	0.530 (C/T vs. surgery)
With C/T					
No	8	25.0%	0.071	25.0%	0.037
Yes	66	36.3%		45.4%	
Surgical management					
No	19	15.8%	0.028	19.7%	0.067
Yes	55	41.8%		50.9%	
Emergency operation[a]					
No	59	37.2%	0.260	43.9%	0.250
Yes	15	26.7%		40.0%	
R0 resection					
No	35	16.7%	0.003	28.1%	0.037
Yes	39	51.3%		56.4%	
Gross resection (R0 + R1 resection)					
No	27	11.1%	0.001	21.6%	0.008
Yes	47	48.9%		55.3%	

C/T: chemotherapy; GI: gastrointestinal; IPI: International Prognostic Index; LDH: lactate dehydrogenase.
[a] All emergency operations were for perforations.

patients received combined therapy had better 1-year OS and PFS rate ($P = 0.016$ and $P = 0.007$, respectively). Accordingly, combined therapy is still the optimal management strategy for small intestinal lymphoma. Regarding surgical procedures, partial resection or open biopsy is not recommended and gross resection of main lesions should be prioritized over achieving margin-free status.

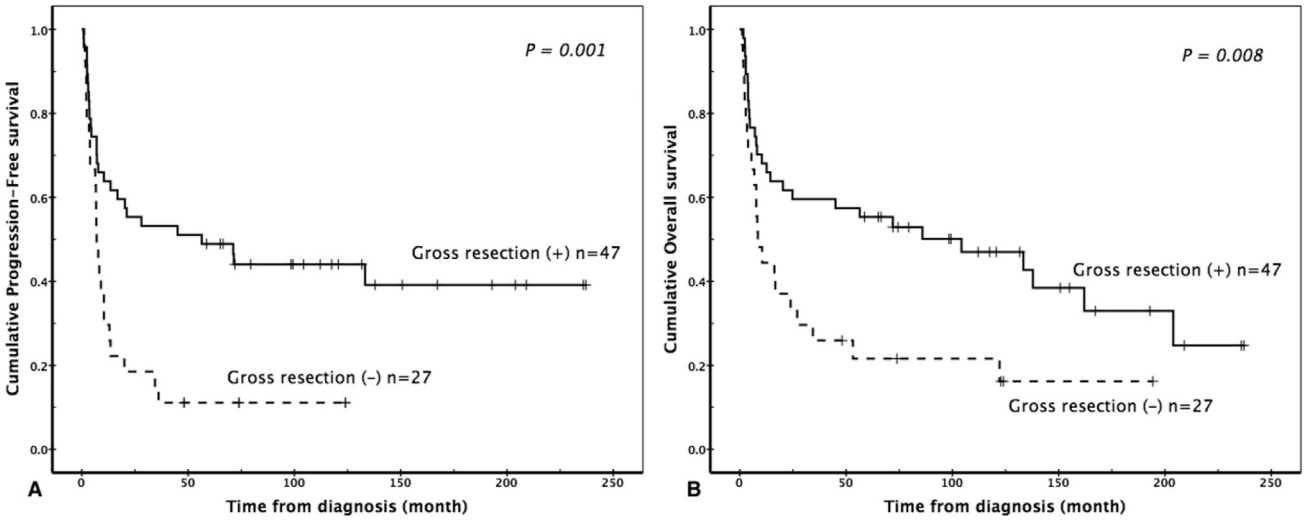

Figure 1. Progression-free survival (A) and overall survival (B) for primary small intestinal lymphoma with or without gross resection.

Table 4
Prognostic factors for progression-free survival (PFS) and overall survival (OS) (Multivariate analysis).

Factors	5-year PFS		5-year OS	
	P	Hazard ratio (CI 95%)	*P*	Hazard ratio (CI 95%)
Primary status				
Age ≥ 65	NS	–	0.010	2.441 (1.233–4.833)
T-cell lymphoma	0.000	15.911 (5.654–44.775)	0.000	16.407 (5.733–46.955)
Ann Arbor stage III or IV	NS	–	0.000	4.337 (2.137–8.805)
IPI score 2 or more	0.001	3.586 (1.714–7.503)	NS	–
Management				
Without gross resection	0.000	6.409 (2.699–15.219)	NS	–
Surgery or chemotherapy alone	NS	–	0.001	4.132 (1.817–9.397)

CI: confidence interval; IPI: Internal Prognostic Index; NS: not significant.

The use of surgery has always been restricted in GI tract lymphoma because it may result in serious complications. Some patients with GI lymphoma underwent surgery to obtain adequate tissue for pathologic confirmation, while in others, the main reason was to manage tumor-related complications (obstruction, bleeding, and perforation). In most cases, emergency surgery was associated with higher mortality and morbidity. In our series, 38 of 62 patients (61.3%) underwent surgery for tumor-related complications. Among these, 18 (29.0%) were for bowel perforation and all patients with bowel perforation received emergency surgery. Severe surgical complications, including leakage from anastomosis (n = 2), abscess formation, prolonged peritonitis (n = 2), severe infection, and post-operative ileus due to volvulus, occurred in seven patients (11.3%). Of these, six received surgery for tumor-related complications and three underwent emergency surgery. In our study, early mortality was documented in eight patients, and no significant associations were observed between early mortality and emergency surgery, complications, or radical or gross resection. However, three of the patients with severe surgery-related complications died early ($P = 0.026$). Overall, patients who underwent emergency surgery for tumor-related complications were in poorer general condition compared with those who underwent elective surgery. Thus, their risk of death and post-operative complications increased. In the present study, no significant differences in early mortality or severe surgery-related complications were detected that depended on the indication for surgery or type of surgical procedure Moreover, our data indicate that patients who underwent elective or non-complicated surgery, or limited procedures for small intestinal lymphoma, faced similar risks of early mortality/complications of surgery. Possible reasons for these observations might include compromised nutritional status and immunity, and a poorer general condition before more advanced disease progression and onset of complications. Therefore, although surgery influences prognosis, caution should be exercised for all patients with small intestinal lymphoma, with an emphasis on intensive post-operative care.

The major clinical manifestations of small intestinal lymphoma in this study were abdominal pain, bleeding, and obstruction. According to recent publications, the 5-year OS of primary intestinal lymphoma was 53–86.4%.[8,10,24–27] In the present study, 5-year PFS and

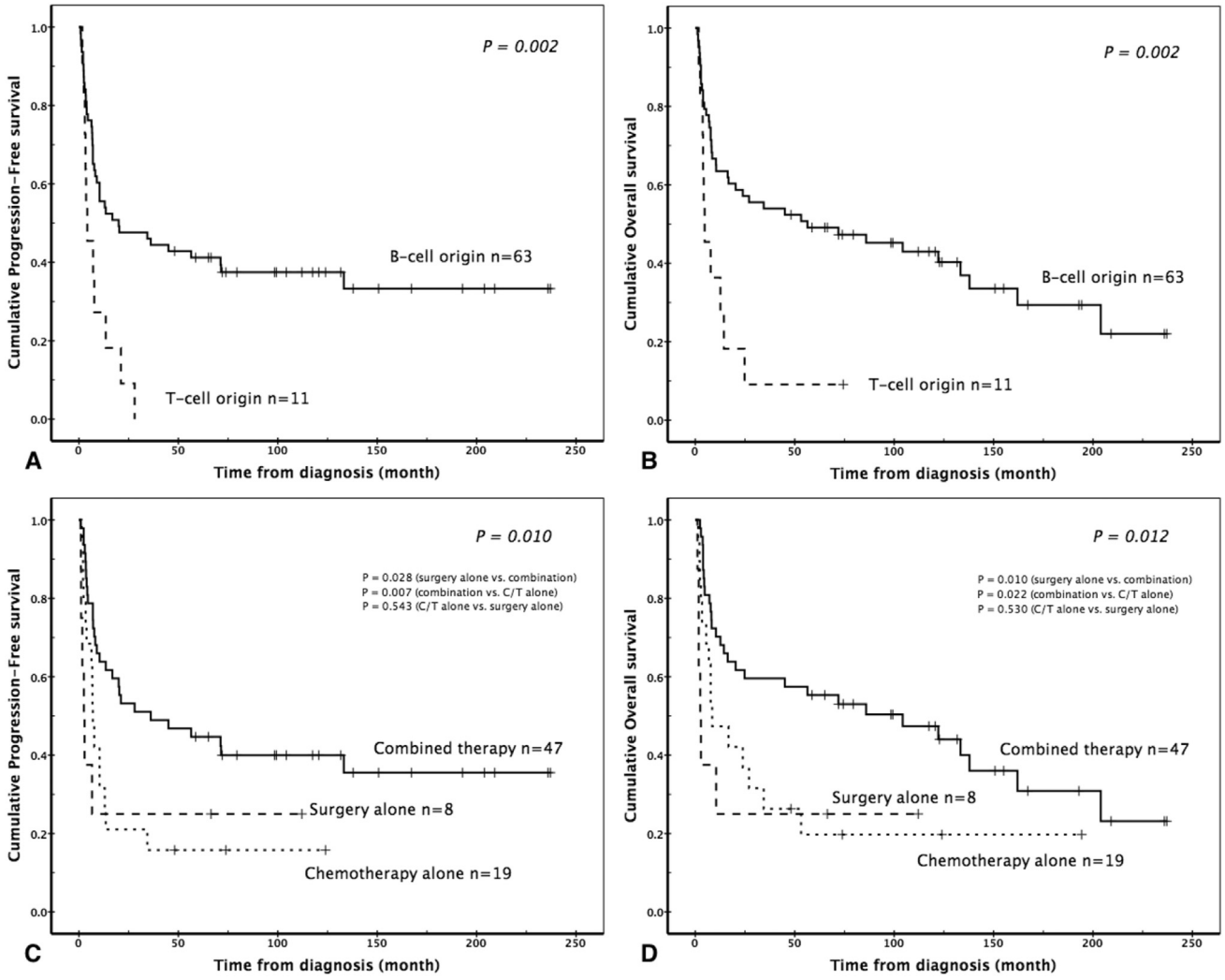

Figure 2. Kaplan–Meier curves of progression-free survival (PFS) and overall survival (OS) for primary small intestinal lymphoma in relation to prognostic factors. Effect of immunophenotype on (A) PFS and (B) OS. Effect of treatment modality on (C) PFS and (D) OS.

OS were 35.1% and 43.2%. The 5-year OS for patients with IPI scores of 0 or 1 was 72.6% in our series (consistent with what would be predicted based on IPI scores), indicating that the clinical management of these patients was good. Our finding that 5-year survival was poorer in patients with small intestinal lymphoma was probably related to difficulties in diagnosis or screening. Endoscopy of the upper and lower parts of the GI tract is widely practiced in most countries. Thus, lesions in the stomach and colon, including lymphoma, can be found and managed at an earlier clinical stage. Although the incidence of duodenal lesions is relatively low – accounting for approximately 5–10% of all primary intestinal lymphoma[8,25] – these may be classified as being located in the stomach, yet their position and size may make them a lot more difficult and complex to treat. In the present study, only two patients had solitary duodenal lymphoma. It is unclear if duodenal lymphoma should be classified as gastric lymphoma, small intestinal lymphoma, or as an independent group for which more information and case numbers are needed to clarify its characteristics, pathophysiology, and optimal treatment modality.

Our study has some limitations. Firstly, the study period was extended because of limited patient numbers included in the original analysis, and discrepancies in medical care might have an impact on the results. Secondly, our analysis did not differentiate between different chemotherapeutic regimens. In addition, five patients received radiation therapy and our study design did not make provision for differences in dose of radiation, clinical effects or related complications. To assess the possibility of such effects on prognosis, further investigations are needed based on a greater number of cases.

Conclusion

Although this study is retrospective and based on a limited number of patients, the data indicate combined therapy with surgery and chemotherapy as an independent

prognostic factor for survival. Gross resection is the recommended surgical procedure for patients with small intestinal lymphoma, improving PFS without a significant increase in the risk of complications. Unlike other GI malignancy, emergency surgery for complications of small intestinal lymphoma does not lead to poor prognosis. Although surgery can be beneficial, caution is warranted as the compromised general condition of patients is accompanied by a high risk of post-operative complications and the potential for early mortality.

Author contributions

Hong YW and Kuo IM contributed to data collection, preparation of the manuscript, editing of the manuscript, and are the primary writers of the manuscript. Liu YY contributed to the review and revision of the manuscript. Yeh TS contributed to the design of the study, the acquisition of data, and coordination of the study.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or th e review of, the manuscript entitled.

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