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Upfront Surgery for Small Intestinal Non-Hodgkin's Lymphoma

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Abstract. *Background/Aim: The clinical significance of surgery for secondary small intestinal non-Hodgkin's lymphomas (NHL) remains unknown. This study aimed to investigate the efficacy of resection for both primary and secondary small intestinal NHL. Patients and Methods: Twenty patients with small intestinal lymphoma who underwent surgical resection at our Institute between 2009 and 2017 were retrospectively evaluated. The clinicopathological and surgery-related factors were reviewed. We also analyzed their surgical outcomes such as postoperative complications, perforation rate, and overall survival (OS). Results: In total, 13 (65%) and 7 (35%) patients had primary and secondary lymphomas, respectively. A total of 70% of patients were diagnosed with aggressive-type lymphomas. A total of 15 (75%) patients had Lugano system stage IV. Only one (5%) patient experienced postoperative grade II deep vein thrombosis and pulmonary embolism. The 3-year OS rate after surgery was 59.6%. Conclusion: Surgical resection prior to chemotherapy is a feasible and safe therapeutic strategy for small intestinal NHL.*

The incidence of primary extranodal non-Hodgkin's lymphoma (NHL) has increased in recent years. Primary gastrointestinal lymphoma is the most common type of extranodal NHL, accounting for 30-45% of all cases (1-4). With respect to tumor location, the small intestine is the second most frequent site of gastrointestinal lymphomas (20-35%) after the stomach (55-70%) (3, 5, 6). Primary gastrointestinal NHL is less common than secondary gastrointestinal involvement of nodal lymphomas (7, 8). Small intestinal NHL is easily misdiagnosed until serious complications occur, such as perforation and ileus. Furthermore, the optimal treatment for small intestinal NHL remains controversial, and the prognosis is unsatisfactory, furthermore any large-scale investigation is difficult due to disease rarity and complicated histological subtypes (8, 9).

Perforation is a complication associated with high mortality rates, and 1-25% of gastrointestinal lymphoma patients receiving chemotherapy develop perforation (10-12). In patients with small intestinal lymphomas, approximately 50% of perforations occur during chemotherapy. Moreover, perforation is more frequent in small intestinal NHL than than NHL of any other sites (11). Combination treatment of surgery and chemotherapy was reported to provide better survival outcomes than chemotherapy (13, 14) or surgery alone (15) in primary intestinal NHL. Surgery prior to chemotherapy helps improve safety and completion of chemotherapy because it can prevent chemotherapy-related perforation (11). However, the clinical significance of surgery prior to chemotherapy has not been fully investigated for NHL that is not confined to the small intestine. This study aimed to investigate the surgical outcomes of patients with NHL involving the small intestine regardless of disease distribution.

Patients and Methods

We retrospectively evaluated 20 consecutive patients with small intestinal NHL who underwent surgery between September 2009 and April 2017 at the Department of Surgical Oncology, The University of Tokyo. Since 2009, NHL patients who had gastrointestinal symptoms, were at high risk of perforation, and/or were in need for diagnosis were indicated for surgery by a multidisciplinary team that included hematologists and surgeons in our hospital. We analyzed their demographic data, symptoms, laboratory data at diagnosis such as serum lactate dehydrogenase and interleukin-2 receptor levels, histological features, stage, major diameter of tumor, surgical approach and procedure, postoperative complications graded according to the Clavien-Dindo classification (16), introduction rate of chemotherapy, perforation rate after initiation of chemotherapy, and postoperative overall survival (OS).

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Key Words: Small intestinal lymphoma, prevention of perforation.

Table I. *Patient characteristics*.

	Number (%)
Age ≥60 years	14 (70%)
Male	10 (50%)
ECOG performance status ≥2	2 (10%)
Hemoglobin ≤10 mg/ml	8 (40%)
LDH >upper normal limit	4 (20%)
sIL-2R >500 U/ml	15 (75%)
Albumin ≤3.0 mg/dl	4 (20%)
Primary lymphoma	13 (65%)
Main symptoms	
Abdominal pain	7 (35%)
Intestinal bleeding	4 (20%)
Subcutaneous tumors	3 (15%)
Edema	1 (5%)
Malaise	1 (5%)
None	4 (20%)

ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase, sIL-2R: soluble interleukin-2 receptor.

Table II. *Histology and stage classification of patients*.

Histology	
B-cell lymphoma	
Diffuse large B-cell lymphoma	10 (50%)
Follicular lymphoma Grade 2	1 (5%)
Follicular lymphoma Grade 3a	1 (5%)
Mantle cell lymphoma	4 (20%)
Burkitt lymphoma	2 (10%)
T-cell lymphoma	
Enteropathy-associated T-cell lymphoma	2 (10%)
Lugano stage (1994) for 14 primary lymphomas	
I	3 (21%)
II1	2 (14%)
II2	0 (0%)
IIE	0 (0%)
IV	9 (65%)
Lugano stage (2014) for 6 secondary lymphomas	
I	0 (0%)
II	0 (0%)
III	0 (0%)
IV	6 (100%)
IPI score of 14 patients with the aggressive lymphoma	
0 or 1	2 (14%)
2	5 (36%)
3	4 (29%)
4 or 5	3 (21%)

IPI: International prognostic index.

Table III. *Surgical treatment of patients*.

Surgical procedure	
Partial resection	11 (55%)
Ileocecal resection	7 (35%)
Right hemicolectomy	2 (10%)
Surgical approach	
Laparoscopic surgery	8 (40%)
Open surgery	12 (60%)

The diagnostic modalities included bilateral bone marrow aspiration and biopsy, computed tomography scans from the neck to the pelvis, whole-body positron emission tomography, double balloon endoscopy, and/or small bowel radiography. Histological classification was based on the World Health Organization (WHO) classification (17). The International Prognostic Index (IPI) score (18) was reviewed in cases of aggressive lymphomas. Primary or secondary intestinal lymphoma was defined according to the Lewin criteria (19). Staging was done according to the Lugano criteria 1994 (20) and 2014 (21) for primary and secondary lymphoma, respectively. Overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause. OS curve was estimated using the Kaplan-Meier method. This study was approved by the Ethics Committees of the University of Tokyo [No. 3252-(8)].

Results

Clinicopathological characteristics. Among the 20 patients, 10 were men and 10 were women. The median patient age was 74 years (range=21-80 years) (Table I). Overall, 13 (65%) and 7 (35%) patients were diagnosed with primary and secondary small intestinal lymphoma, respectively. There were 3 (15%) patients who had multiple gastrointestinal lymphoma (*e.g.*, transverse colon lymphoma or duodenum lymphoma simultaneously). The most frequent macroscopic type was ulcerative type (n=16, 80%), followed by bulky type (n=3, 15%), and unclassified (n=1, 5%). The most frequent symptom was abdominal pain (n=7, 35%), followed by overt or occult bleeding (n=4, 20%). The median tumor size was 7.8 cm, excluding two patients with diffuse infiltrative type lymphoma. Lymphoma was located in the ileum, jejunum, and both in 15 (75%), 4 (20%), and 1 (5%) patient, respectively. Diffuse large B-cell lymphoma (DLBCL) was the major histological subtype (50%) (Table II). In total, 15 (75%) patients had Lugano stage IV disease, and 14 patients (70%) had aggressive lymphoma or highly aggressive lymphoma according to the WHO classification. The IPI score of these patients is shown in Table II. Patients were almost equally distributed among the low, low intermediate, high intermediate, and high-risk groups.

Treatment and outcomes. Table III summarizes the surgical treatments. Overall, 8 (40%) patients were treated *via* a laparoscopic approach, and 7 (35%) underwent complete lymphoma resection. One male patient developed Clavien-Dindo Grade II deep vein thrombosis and pulmonary embolism after surgery, but he recovered *via* conservative thrombolytic therapy. This might have been caused by the

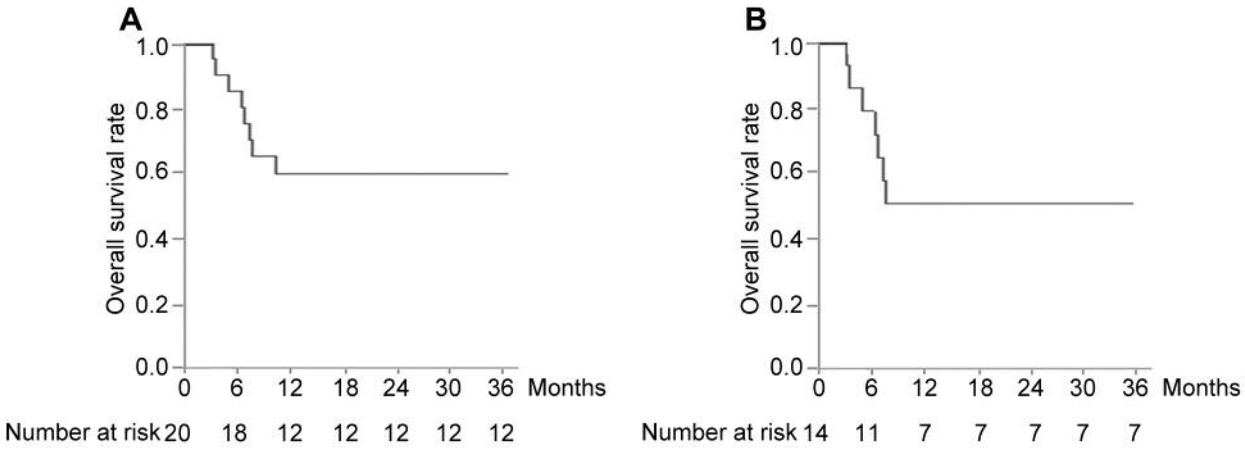

Figure 1. *(A) The overall survival (OS) curve for all 20 patients. The three-year OS rate was 59.6%. (B) The OS curve for 14 patients with aggressive lymphoma. The three-year OS rate was 50.0%.*

long operative time needed for resecting six segments for 11 lesions located in both the jejunum and the ileum. Chemotherapy was initiated on day 28 after surgery in this patient. In all patients, chemotherapy was initiated after a median interval of 29 postoperative days. There was no intestinal perforation during and after the chemotherapy.

The median follow-up time was 27 months. The OS curve for all 20 patients is shown in Figure 1. The 3-year OS rate for all patients was 59.6%. Meanwhile, the OS curve for the 14 patients with aggressive lymphoma is shown in Figure 1B. Their 3-year OS rate was 50.0%. The median follow-up time was 27 months. The OS curve for all 20 patients is presented in Figure 1A. The three-year OS rate for all patients was 59.6%. The OS curve for 14 patients with aggressive lymphoma is shown in Figure 1B. Their three-year OS rate was 50.0%.

Discussion

In the current study, we investigated the outcomes of surgery prior to chemotherapy for primary and secondary small intestinal NHL regardless of disease distribution. The condition of patients with aggressive-type NHL may worsen rapidly if surgery-associated complications postpone the initiation of chemotherapy. Thus, we specifically investigated whether surgical resection prior to chemotherapy has a negative impact on the prognosis of patients with small intestinal NHL. Only one patient developed grade II complications. The interval between surgery and chemotherapy in this patient was 28 days, which is similar to that in the overall cohort (median: 29 days).

Chemotherapy with or without radiotherapy has been established as the standard treatment modality for gastric DLBCL (22, 23). In contrast, there is no clear consensus on the optimal treatment modality for extranodal small intestinal NHL, particularly secondary NHL of the small intestine (14). Furthermore, chemotherapy for small intestinal NHL occasionally induces perforation. Perforation during chemotherapy is life-threatening, with a reported mortality rate of over 30% (11). Moreover, although several studies have reported the efficacy of surgery before chemotherapy for primary small intestinal NHL with respect to prevention of perforation and tumor reduction (13), the therapeutic value of surgery before chemotherapy in patients with secondary small intestinal NHL is yet to be determined.

In the current study, the 3-years OS rate was 59.6% for the entire population in which 70% had aggressive lymphoma, and 75% stage IV disease. In the past, Kobayashi *et al*. reported that the 5-year OS rate for 19 small intestinal lymphoma patients who did not undergo surgery was 72.2%; however, only 1 of the 19 (5.3%) patients had stage IV disease (24). Zhai *et al*. evaluated 46 small intestinal lymphoma patients, 30.4% of whom had stage IV, and reported a 5-year OS rate of 64.2% (10). In their study, 29 patients (63.0%) underwent surgery. Moreover, the 3-year OS rate for 14 patients with aggressive lymphoma (10 patients had stage IV disease) was 50.0% in our cohort. Kim *et al*. reported a 3-year OS rate of 44% for 25 patients with stage IV DLBCL involving the stomach, small, or large intestine who underwent surgery and chemotherapy (25). Collectively, we guessed that the survival outcomes of our patients might be acceptable although it was hard to compare them with the aforementioned reports. Importantly, there was no intestinal perforation during and after chemotherapy in the current cohort.

However, several limitations of this study should be considered when interpreting our results. First, the study had a retrospective design with a small sample size recruited

from a single institution. Second, various subtypes and stages of small intestinal NHL were included. Moreover, this study did not include non-surgical cases of small intestinal NHL. Our results could not be directly compared with other literatures because patients' backgrounds, treatments, and outcome measures were not matched. Further studies are needed to establish the optimal treatment modality for small intestinal NHL.

In conclusion, our results indicated that surgical resection prior to chemotherapy is an effective treatment modality for both primary and secondary small intestinal NHL. Correct diagnosis and multimodal treatment by a multidisciplinary team of surgeons, hematologists, gastroenterologists, and radiologists are crucial in the management of small intestinal NHL.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Tetsuhiro Iida, Hiroaki Nozawa, and Kazuhiro Toyama designed the study and wrote the initial draft of the manuscript. Hirofumi Sonoda, Mineo Kurokawa, and Soichiro Ishihara contributed to data analysis and interpretation. Kazushige Kawai, Keisuke Hata, Toshiaki Tanaka, Takeshi Nishikawa, Kazuhito Sasaki, Yasutaka Shuno, Manabu Kaneko, Koji Murono, Shigenobu Emoto, and Hiroshi Ishii have contributed to data collection. Kazushige Kawai, Keisuke Hata, Toshiaki Tanaka, Takeshi Nishikawa, Kazuhito Sasaki, Yasutaka Shuno, Manabu Kaneko, Koji Murono, Shigenobu Emoto Hiroshi Ishii, Mineo Kurokawa, and Soichiro Ishihara critically reviewed the manuscript. All authors approved the final version of the manuscript and agree 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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