

Gastrointestinal Lymphoma—A Review of 54 Patients in Singapore

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Abstract

Primary gastrointestinal (GI) lymphoma accounts for 2% to 5% of all GI malignancies. Primary therapy in uncomplicated GI lymphoma remains controversial.

Fifty-four patients (male to female ratio of 4:3, median age 56 years) with GI lymphoma were studied to evaluate complications and results of therapy. The sites involved were the stomach (31), small bowel (12), large bowel (4), gallbladder (1) and multifocal (6). Distribution by stage and grade (Working Formulation or Kiel) were: IE-30%, IIE-43%, IIIE-6%, IV-20% and unknown-I %; low grade-33%, intermediate grade-59% and high grade-8%. Majority (54%) had diffuse large cell lymphoma. Twenty-three patients (43%) underwent primary resection of the tumour followed by chemotherapy in 14 or radiotherapy in 3. Seventeen patients (31%) had primary chemotherapy and 3 (6%) had primary radiotherapy. Of the 48 patients who underwent therapy, 52% had complete response. At the last follow-up (median 21 months), 25 patients were disease-free. Overall survival was 67% at two years.

Treatment strategies employing surgery, radiotherapy and chemotherapy, alone or in combination, do not appear to influence outcome. Surgical resection plus chemotherapy appear to be effective in the control of local and distant disease.

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Introduction

Primary gastrointestinal (GI) non-Hodgkin's lymphoma represents the most common extranodal site of non-Hodgkin's lymphoma.^{1,2} GI lymphoma is defined as the presence of either obvious predominantly gastrointestinal lesions or symptoms at presentation, proven histologically to be caused by gastrointestinal involvement with lymphoma.³ About half of primary GI lymphomas arise from the stomach, with the small intestine and colon being less common.^{2,4}

Unlike primary adenocarcinoma of the GI tract where surgery has long been established and remains the primary modality of therapy, the treatment modalities available in GI lymphoma include surgery, radiotherapy, chemotherapy and their different combinations. The difference lies in the high radio- and chemosensitivity of

this malignancy. The treatment offered for GI lymphoma has evolved significantly from surgery being the only treatment to chemotherapy alone.

As the number of patients with GI lymphoma seen in any one institution is limited, it is often difficult to conduct randomised comparative studies to evaluate the role of the three modalities in management. Most of the knowledge in its treatment stems from institutional retrospective evaluations and prospective phase II studies. Until the results of multicentre studies are available, the standards of practice may vary significantly among institutions and medical practitioners.

The objective of this paper was to review all patients with GI lymphoma presented at our institution's regular lymphoma meeting. Before 1990 only selected patients with lymphoma were presented, but since 1990 all lym-

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phoma patients have been presented for discussion and consensus on management. This paper reports our analysis of 54 patients with GI lymphoma at our institution between 1983 and 1993.

Patients and Methods

The medical records of all patients diagnosed to have GI lymphoma were reviewed to evaluate the patient characteristics, clinical presentation, histological subtypes, treatment and disease outcome. Histology was classified according to the Working Formulation.⁵ Histologic subtypes not included in the Working Formulation were classified using modified Kiel classification.⁶ All cases were reviewed by two consultant pathologists (IS, CMF). Forty-eight patients had histological slides available for review. Patients were staged according to Ann Arbor classification. Staging investigations included history and physical examination, chest X-ray, computerised tomography of the abdomen (after 1985), bone marrow examination, haemogram, and renal and liver function tests. For patients diagnosed to have GI lymphoma before 1985, staging was attempted during surgical resection of the tumour as computerised tomography was unavailable. Bipedal lymphangiography was not routinely done.

Results

Patient Characteristics

Of the 54 patients, 31 were male (Table I). The median age was 56 years (range 17 to 92 years). The majority of patients had disease confined to the GI site and regional lymph nodes (Table II). Despite the majority having "localised" disease, 44% of them had "B" symptoms.

Abdominal pain was the presenting symptom in 30

(56%) of the patients. Other presenting symptoms included mass (7%), "B" symptoms (7%), symptomatic anaemia (5%), GI obstruction (5%), GI bleeding (4%), chronic diarrhoea (2%) and non-specific vomiting (2%). The presenting symptom was not documented for 6 patients. Three patients had concomitant or previous history of malignancy (stomach cancer, colon cancer and renal cell carcinoma); all had low-grade GI lymphoma.

The commonest site of GI involvement was the stomach (58%). This was followed by the small intestine (22%) and colorectum (7%). Six patients (11%) had multifocal involvement within the GI tract. One patient had lymphoma of the gallbladder. Majority of the patients had aggressive lymphoma (Table II); the most common histology was diffuse large cell lymphoma (26/48 patients, 54%). Low grade lymphoma was not uncommon (16/48 patients, 33%).

Among patients with gastric lymphoma, the median age was 55 years. Nineteen (66%) were of diffuse large cell histology. Only 8 (26%) of the 31 patients with gastric lymphomas were above 60 years old. About half (52%) the patients with gastric lymphoma were female. Small bowel lymphomas were of low-grade histology in 5/11 (45%) and diffuse large cell lymphoma in another 5 (45%) patients. The median age of patients was 59 years. The majority of patients with small bowel lymphoma were male (83%).

Treatment

The primary treatment is presented in Table III. One patient who underwent surgery, chemotherapy and radiotherapy is not represented in the table.

Seventeen out of the 54 patients (31%) underwent primary chemotherapy alone after histologic diagnosis. Two (2/17) patients developed GI perforation during primary chemotherapy; both had not undergone prior resection of the primary GI lymphoma. One patient had stage IVB disease and was not a candidate for surgical

TABLE I: PATIENT CHARACTERISTICS

Number of patients	54
Male	31
Female	23
Median age (years)	56
Range (years)	17 to 92
Stage	
IE	16
IIE	23
IV E	11
Unknown	1
B symptoms present	24
Site of tumour	
Gallbladder	1
Stomach	31
Small bowel	12
Large bowel	4
>1 gastrointestinal site	6

TABLE II: HISTOLOGY AND STAGE OF THE PATIENTS

Histology	Stage					Survival (months)
	I	II	III	IV	Unknown	
Small lymphocytic	1	1	0	1	0	4.5-47+
Lymphoplasmacytoid	0	0	0	1	0	42+
MALT	5	4	0	1	0	7-126+
Mantle cell	1	0	1	0	0	25-35+
Centroblastic	0	1	0	1	0	13.5-35-t
Diffuse large cell	7	13	1	4	1	1-116+
Immunoblastic	0	0	1	0	0	2.5
Burkitt	0	2	0	0	0	7.5-110+
Pleomorphic T	0	0	0	1	0	14.5
Unavailable	2	2	0	2	0	2.5-124+

MALT: mucosa-associated lymphoid tissue

TABLEIII: PRIMARY TREATMENT OF PATIENTS WITH GI LYMPHOMA

	Chemotherapy	Surgery	Radiotherapy
Chemotherapy	17	14	4
Surgery	14	6	3
Radiotherapy	4	3	3
Total	35	23	10

resection of the primary tumour in the stomach. At laparotomy for acute abdomen, the perforation site was in the ileum distal to the site of the original gastric lymphoma. Histology of the resected portion of the ileum did not show lymphoma. The other patient had stage IIEB non-bulky gastric lymphoma and had declined initial surgery. During laparotomy for acute abdomen, repair of the perforated site in the stomach was performed. Again, histology of the perforated site did not show lymphoma. Gastrointestinal bleeding as a complication of chemotherapy was not seen.

Fourteen patients underwent surgical resection of the primary tumour followed by chemotherapy. Indications for adjuvant chemotherapy were “B” symptoms, and stage II to IV lymphoma. There were too few patients with stage I to II primary GI lymphoma receiving either chemotherapy alone or surgery followed by chemotherapy to comment on the role of surgery in early stage GI lymphoma. Doxorubicin containing combination chemotherapy was administered to 29 of the 36 patients who received chemotherapy as either primary or adjuvant therapy.

Six patients underwent surgical resection alone and 3 patients received radiotherapy alone. Six patients were not treated after diagnosis; 3 had low-grade lymphoma and 3 were elderly with high-grade lymphoma. Twenty-five of the 48 patients who received treatment achieved complete clinical and radiological response by the end of therapy.

Outcome

Two patients were lost to follow-up at 5 and 50 months, respectively. Both were disease-free at the last follow-up. Median follow-up of the remaining 52 patients was 21.1 months (range 3.6 to 108.6 months). Eighteen patients have died, 13 of lymphoma or treatment-related complications and 5 of non-related causes. There was only one lymphoma-related death beyond 24 months. The estimated overall 2-year survival (Kaplan-Meier life-table analysis) was 67%. Twenty-five were disease-free at the time of the last follow-up. Six patients recurred at 6, 15, 25, 30, 39 and 55 months, respectively. The sites of recurrence were GI (2), regional nodes (2), brain (1) and lung (1). One patient was alive and disease-free after salvage chemotherapy, two patients died with

disease and the other 3 were alive with disease.

Discussion

The anatomic distributions of gastrointestinal lymphoma in this series were: stomach 58%, small bowel 22%, large bowel 7% and multifocal GI involvement 11%. This is consistent with other reports.^{1,2,4} Diffuse large cell type lymphoma was the most common (54%). Although the majority of patients (72%) had localised stage I-II disease, 44% of patients had “B” symptoms, possibly because of weight loss resulting from gastrointestinal disease. In patients with gastrointestinal lymphoma, weight loss resulting in “B” symptoms may not have the same significance as in patients with nodal lymphomas.

Two patients had concomitant GI small lymphocytic lymphoma and GI adenocarcinoma. This raises several postulates as to whether there was some common underlying aetiologic factor. For example, *Helicobacter pylori* has been associated with gastric cancer^{7,8} as well as mucosa-associated lymphoid tissue (MALT) lymphoma.^{9,10} The question of impaired immunity predisposing to two concomitant malignancies also arises.

In gastrointestinal lymphoma the surgeon plays an important role by establishing the diagnosis. However, the role of surgery in the management of primary GI lymphoma remains controversial. A pilot study of 18 patients with stage IE to IV primary gastric lymphoma who underwent complete resection of the primary tumour followed by chemotherapy, reported overall actuarial disease-free survival of 82.6%.¹¹ However, the French have also reported 4-year survival of 85% in patients with gastrointestinal lymphoma undergoing intensive chemotherapy alone.¹² In our series, 11% of patients had multifocal sites of gastrointestinal involvement. This figure could be higher as not all patients were surgically staged. This would argue for the use of adjuvant chemotherapy to eradicate other potential sites of involvement after local treatment such as surgery or radiotherapy.

Chemotherapy has consistently improved overall and disease-free survival in patients with lymphoma.^{13,14} Patients with stage IE and IIE disease had similar survival and disease-free survival rates whether they underwent complete surgical resection or incomplete or no surgical resection prior to chemotherapy.¹³ Studies have suggested that surgical debulking may be omitted without affecting survival.^{2,12,15} Gastrointestinal organ preservation may provide a substantial advantage in the quality of life of these patients.

It has been suggested that surgery may avoid the gastrointestinal bleeding and perforation that have been encountered after chemotherapy.¹¹ The frequency of perforation varies from 1% to 28%.^{11,16,17} In one study of primary gastric lymphoma, bleeding or perforation was

not seen in 30 surgically unresected cases.¹⁸ Mittal et al's review of the literature¹⁹ reported that gastric perforation occurred in only 3 of 75 unresected gastric lymphomas treated with radiotherapy alone. Twenty-five out of 626 patients developed a perforation prior to treatment. These findings suggest that gastric perforation in patients with gastric lymphoma may be due to disease progression. In this current series, two patients developed GI perforation while on chemotherapy. However, at surgical exploration, no tumour was seen and the resected sites of perforation had no histological evidence of lymphoma. One patient perforated in the small bowel, distal to the site of disease presentation.

Surgical resection may still be unavoidable as a diagnostic procedure in a minority of cases and may represent the primary therapeutic procedure in early-stage and low-risk patients, but it cannot be considered mandatory merely for debulking purposes or to obviate possible perforation or haemorrhage. Until a randomised stratified study comparing primary surgery to primary chemotherapy in primary gastrointestinal lymphoma is completed, the optimal therapeutic option for primary gastrointestinal lymphoma remains controversial.

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