

# Prognostic factors in patients with non-Hodgkin's lymphoma presenting with gastrointestinal tract symptoms

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**BH WEINERMAN, B MACDOUGALL, I CARR. Prognostic factors in patients with non-Hodgkin's lymphoma presenting with gastrointestinal tract symptoms. Can J Gastroenterol 1991;5(1):5-10.** Forty-one individuals who presented with symptoms referable to the gastrointestinal tract were extracted from the authors' total review of non-Hodgkin's lymphoma in Manitoba from 1968 through 1978. Only cases at stages I to III were included, and there were 22 males and 19 females. Sixteen non-Hodgkin's lymphomas arose in the small bowel, 15 in the stomach and 10 in the colon. The natural history of this group of gastrointestinal non-Hodgkin's disease is described, and univariate and multivariate analyses were done using the variables of sex, pathology, stage, resection, site of disease and initial chemotherapy. The median survival of the group was 28 months. Sex and stage appeared to be important prognostically, but after multivariate analysis, only the female sex appear to be a good prognostic variable. There was a suggestion that resection should be attempted in these lesions, but there was not a large sample size in this group. In addition, it was felt that this group of individuals followed the same survival pattern as did poor prognosis non-Hodgkin's lymphomas of nongastrointestinal origin.

**Key Words:** GI non-Hodgkin's lymphoma, Prognostic factors

## Analyse des facteurs pronostiques chez les patients atteints de lymphomes non hodgkiniens qui présentent des symptômes impliquant les voies gastrointestinales

**RESUME:** Après avoir effectué une revue totale des cas de lymphomes non hodgkiniens (LNH) relevés au Manitoba de 1968 à 1978, les auteurs ont retenu 41 personnes présentant des symptômes impliquant les voies gastrointestinales.

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IT IS GENERALLY AGREED THAT lymphomatous involvement of the gastrointestinal tract is the most common site of extranodal primary non-Hodgkin's lymphoma involvement (1,2). Several different prognostic factors have been reported in multiple papers, often with differing conclusions (3). Even histological subtypes, generally the most important prognostic factor in systemic disease (4), were found, by some, to be less important than stage or other factors such as lactate dehydrogenase, sex and perforation. One of the questions that arises is whether patients presenting with symptoms referable to the gastrointestinal tract have a different natural history from those with other lymphomas of the same stage and histological type, and whether, in this group, there are any prognostic variables that may be helpful to the clinician. The studies that have examined these questions (2,3,5-7) have not been based on an entire population experience (such as the Manitoba Tumour Registry) or have not been solely confined to people presenting with symptoms.

In view of this, the authors extracted, from their total review of non-Hodgkin's lymphoma in Manitoba from

Seuls les cas de stades 1 à 3 ont été inclus, soit 22 hommes et 19 femmes. Seize LNH ont été décelés dans le grêle, 15 dans l'estomac et 10 dans le côlon. L'histoire naturelle de ce groupe de LNH gastrointestinaux est décrite et des analyses unifactorielles et multifactorielles ont été effectuées (sexe, pathologie, stade, résection, site de la maladie et chimiothérapie initiale). La survie médiane du groupe était de 28 mois. Le sexe et le stade semblaient importants quant au pronostic, mais après une analyse multivariée, le sexe féminin est resté la seule bonne variable pronostique. On a suggéré que la résection de ces lésions devrait être tentée, mais les dimensions de l'échantillon étaient trop réduites dans ce groupe. De plus, on a estimé que les patients étudiés avaient le même profil de survie que les LNH d'origine non gastrointestinale et de mauvais pronostic.

1968-78 (4), those individuals who presented with symptoms referable to the gastrointestinal tract. Symptoms and signs were often not clearly described in the charts, but anyone who presented with an abdominal mass thought to be of gastrointestinal origin, abdominal pain of gastrointestinal origin, or altered bowel function as a presenting complaint, was considered symptomatic. Weight loss by itself was not considered a gastrointestinal symptom. Two patients of the 41 were said to have a history of sprue, not confirmed on biopsy. Material at the time of diagnosis of lymphoma was not re-examined for this condition. Sixteen other patients had examinations of their bowels noted in this review, none of which were noted to be sprue. One patient had benign peptic ulcer, one inflamed gastric mucosa, and one a prominent plasma cell infiltrate. All others were negative.

Cases of gastrointestinal non-

Hodgkin's lymphoma were examined in order to describe their natural history, and to elucidate the survival implications of sex, pathology, stage, resection, site of disease and initial chemotherapy.

#### PATIENTS AND METHODS

The survival of all adult patients with non-Hodgkin's lymphoma from the Manitoba Tumour Registry has been previously reported (4). The authors extracted from this database (473 cases - all adult, age greater than 18 years) individuals who were confirmed by biopsy to have gastrointestinal non-Hodgkin's lymphoma and who presented with gastrointestinal complaints. All pathology slides were reviewed by one of the authors (IC) and, if slides were not available, the case was not included in the analysis (five cases). The cases were classified according to the Rappaport classification (8) and the International Working Formulation (9). Staging followed the Ann

**TABLE 1**  
Main presenting symptoms of patients with gastrointestinal lymphoma

Symptoms	Patients (%)
Abdominal pain	30 (73)
Weight loss	12 (30)
Constipation/diarrhea	17 (41)
Abdominal mass	9 (22)

*Other symptoms included fever (7%), pruritus (2%) and chills/sweats (5%)*

Arbor staging system (10). All patients had histories, physical examinations, chest x-rays, lymphangiograms, liver scans and functions, and bone marrow biopsies, unless these areas were biopsied at laparotomy. Computed tomography scans were not available during this time period. Stage IV lymphomas were excluded, since it could not be determined if these individuals had primary or secondary gastrointestinal involvement, or whether their gastrointestinal symptoms were manifestations of primary nodal stage IV lymphoma. Data on age, sex, resection, radiotherapy, chemotherapy and survival were abstracted. Deaths from other intercurrent illness, unless related to the lymphoma (such as perforation of the gastrointestinal tract or infection secondary to the disease or treatment), were treated as censored information in the life-table analysis plots. If secondary malignancy intervened, survival was calculated up to that time and subsequently censored unless there was clear evidence of progression of the lymphoma. Four patients were censored after they died of other diseases. Three developed secondary malignancies and died. These were: carcinoma of the sebaceous gland nine-and-one-half years later; carcinoma of the endometrium five years later; and carcinoma of the lung six years after diagnosis of lymphoma. One patient died two years after diagnosis with no evidence of lymphoma. Survival plots were determined by the actuarial life-table method (11), and were compared using the log rank or Wilcoxon statistic (11). To identify parameters that predicted survival, multivariate regression analysis was performed (12).

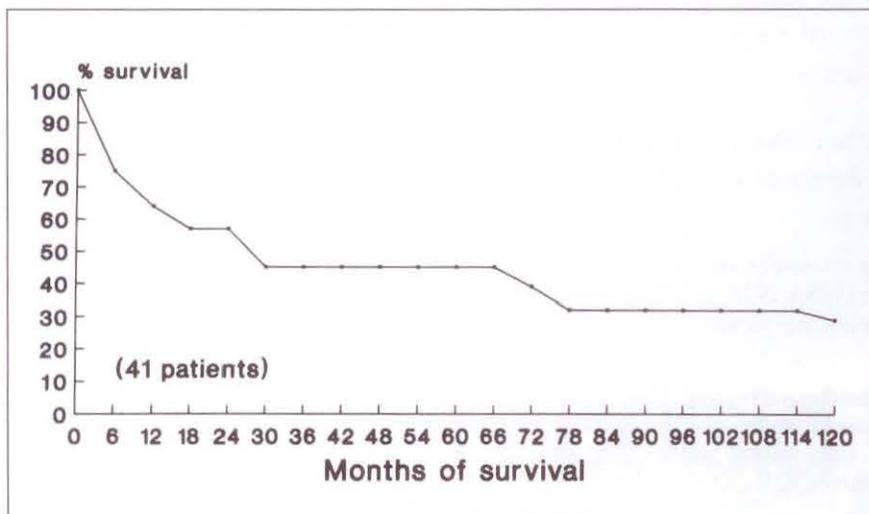


Figure 1) Total group survival of 41 patients with gastrointestinal non-Hodgkin's lymphoma

## RESULTS

Forty-one patients from the total review of 473 non-Hodgkin's lymphomas (1968-77) who presented with gastrointestinal symptoms and had stages I to III primary gastrointestinal lymphomas were identified. All pathology slides were reviewed. Sixteen non-Hodgkin's lymphomas arose in the small bowel (39%), 15 in the stomach (37%), and 10 in the colon (24%). The ages of the patients ranged from 18 to 90 years with a median of 61 and a mean of 59.3. There were 22 males (including one with Turner's syndrome who was not analyzed when examining the effect of sex) and 19 females. Seventy-three per cent of patients presented with abdominal pain, 29% with significant weight loss and 41% with constipation or some combination of diarrhea and constipation. An abdominal mass was noted on physical examination in 22% (Table 1).

The median survival of the entire group was 28 months (95% confidence interval 22 to 34) (Figure 1). Patients were separated into good and poor prognosis groups based on the Rappaport classification. Figure 2 shows the actuarial survival plots of those groups compared to the entire tumour registry population from the same period. There is a suggestion of better survival and a plateau in the good prognosis group, but the numbers are too small to make any firm statement (Wilcoxon's statistics,  $P=0.1$ ). There is no difference in survival between the two poor prognosis groups (gastrointestinal and nongastrointestinal), and they follow similar survival curves, with median survivals of 18 months in the gastrointestinal group and 17 months in the entire group of lymphomas.

When survival curves were plotted according to stage, there were 16 stage I patients with a median survival of 61 months, 19 stage II with a median survival of 12 months, and six stage III (one who was actually stage IV by virtue of a single liver nodule on laparotomy) with a median survival of nine months. There was a suggestive difference in survival between stage I and stages II and III, but this did not reach statistical significance ( $0.05 < P < 0.1$ ) (Figure 3).

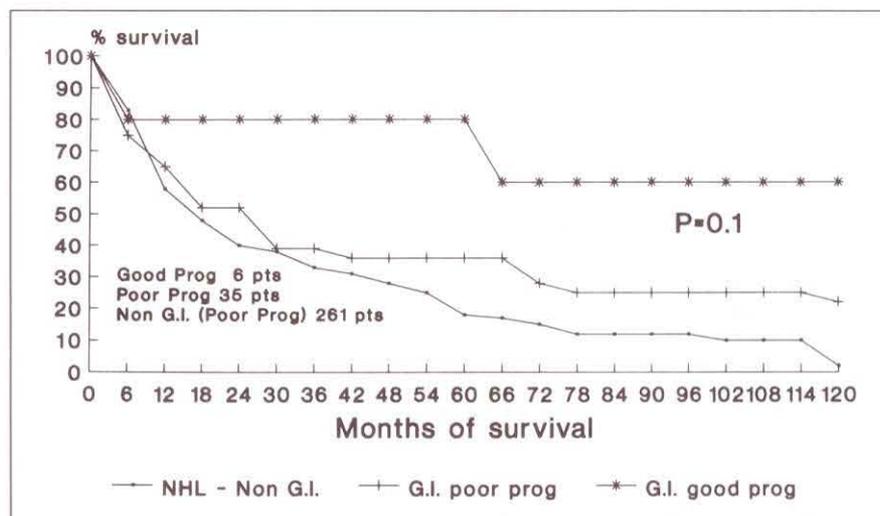


Figure 2) Actuarial survival plots of good versus poor prognosis groups based on the Rappaport classification

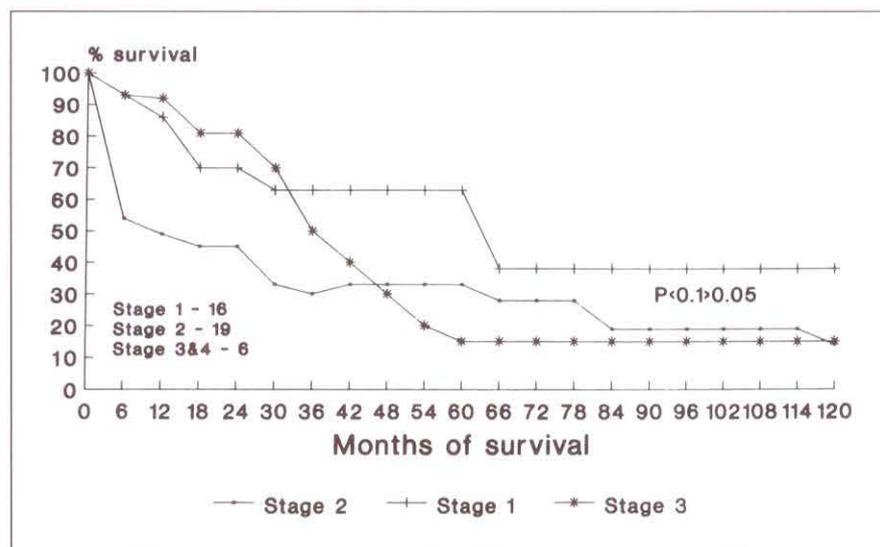


Figure 3) Actuarial survival plots of patients with stage I, II or III disease

When the lymphomas were analyzed using sex as the variable there was a significant difference in survival. Females had a median survival of 66 months and an apparent plateau at that level, while males experienced a median survival of 12 months ( $P=0.02$ ) (Figure 4). Four of the six 'good prognosis' patients were in the female group, as were 10 of the 16 stage I patients. Extracting the 'good prognosis' patients from both groups did not materially change the survival curves, although the median survival for the female group was attained at 60 rather than 66 months. Statistical significance remained at  $P=0.02$ .

Age was not a factor, with most of

the patients being in the older age group.

Seventeen of 41 patients received radiotherapy either combined with surgery, or alone as primary treatment. This did not appear to be a significant factor in survival, but the number of cases were too few to make a statement.

There was no difference in survival in patients who were primarily resected ( $P=0.1$ ) (Figure 5), although only 12 were not resected and hence the sample was small. Seven of the 41 patients developed perforation soon after initial presentation: four of 12 in the non-surgical group, and three of 29 in the surgically resected group. Three of the seven perforated patients died with sep-

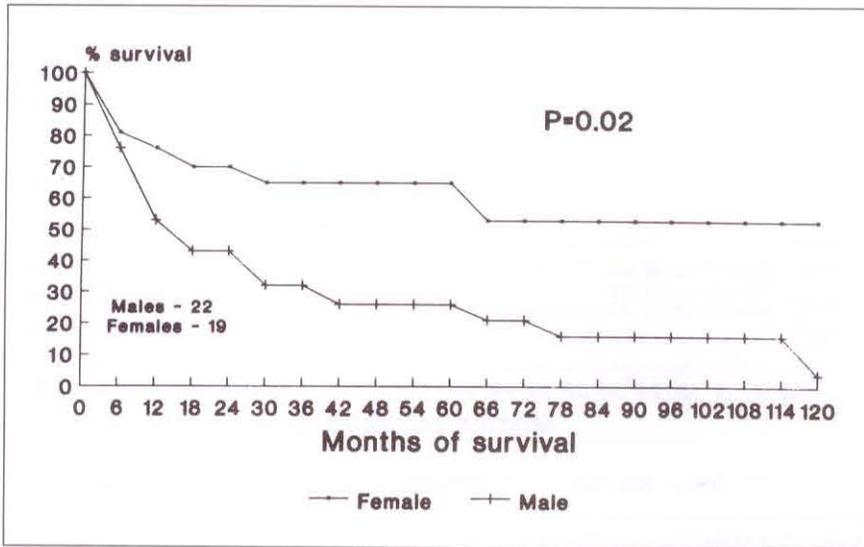


Figure 4) Actuarial survival plots of males versus females with gastrointestinal lymphomas

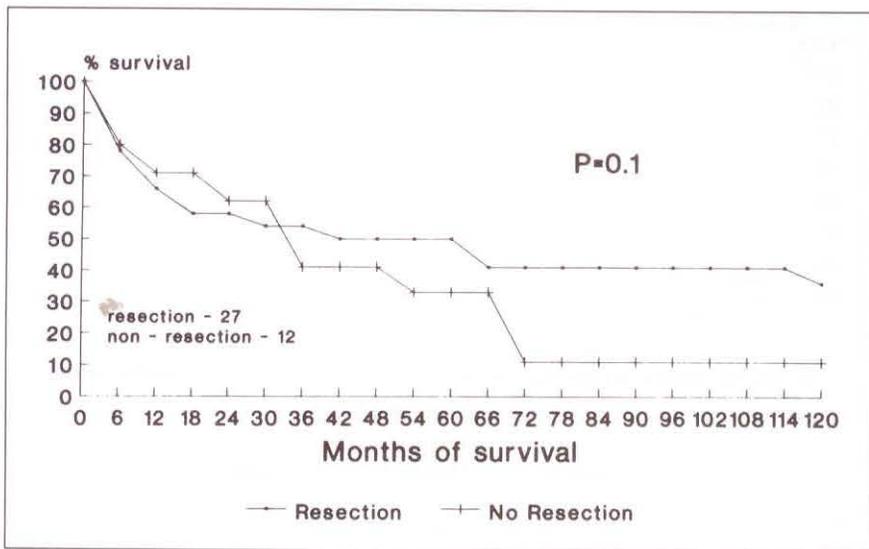


Figure 5) Actuarial survival plots of patients with gastrointestinal lymphomas with resection versus no resection

sis and complications following the surgery (Table 2).

The site of lymphoma was also examined, and this did not correlate with

survival ( $P=0.8$ ) (Figure 6). Initial chemotherapy versus no initial chemotherapy was also examined. There was, in fact, a tendency for the group receiv-

ing initial chemotherapy to do worse, with a  $P$  value between 0.05 and 0.1 (Figure 7).

The six prognostic variables used were all compared in a univariate fashion using the log rank test (11). The variables which seemed to show some prognostic importance (sex, stage and initial chemotherapy) were considered in the proportional hazards regression model (12). By this method only female sex appeared to be an independent variable in prognosis.

### DISCUSSION

The authors reviewed 41 non-Hodgkin's lymphoma patients extracted from a tumour registry, who presented with gastrointestinal complaints. They restricted the analysis to patients who had stages I to III non-Hodgkin's lymphoma. In univariate analysis only female sex, lesser disease stage, and resection of the primary were important in predicting improved survival. In multivariate analysis only female sex was important (12).

Primary lymphomas of the gastrointestinal tract are relatively rare (2,13), although the gastrointestinal tract is frequently involved as a secondary site in widespread lymphomas (1). Many articles have identified important prognostic variables on review of their cases, including clinical stage, age, sex, initial presentations with perforations, erythrocyte sedimentation rate, tumour size, primary gastrointestinal site, histological grade (1-3,5,7,8) and the addition of radiotherapy (6) or chemotherapy (14). The authors wondered if by restricting cases to individuals who clearly presented with gastrointestinal symptoms, a more specific pattern would emerge. Unfortunately, the resulting sample size was small, and nothing emerged as significant other than female sex.

Aozasa *et al* (15,16) reported a poorer prognosis for males, but others have not reported this (3). This poorer prognosis was a definite pattern in the present results which cannot be explained by any other variable.

Some authors have advocated resection of the primary before definitive therapy to avoid possible perforation

TABLE 2  
Perforations at presentations

Location	Initial treatment	Outcome
Stomach	Radiotherapy	Died <1 month of sepsis
Stomach	Radiotherapy	Died <1 month of sepsis
Small bowel	Surgery	Died <1 month of sepsis
Small bowel	Chemotherapy	Died <1 month of sepsis
Small bowel	Surgery and chemotherapy	Alive 5+ years
Small bowel	Surgery and chemotherapy	Alive 7+ years
Colon	Radiotherapy	Alive 5+ years

Sepsis occurred following treatment and in each case was ascribed to probable perforation because of patient symptoms and the gastrointestinal organisms involved

(2). A high percentage of the present nonresected cases perforated (three of 12), but this did not reach statistical significance, and the selection that went into the choice of therapy is unknown. Nevertheless, it is the authors' impression that resection should be strongly recommended in this group of patients, since 25% of the nonresected group perforated compared to 10% of the resected group.

The finding that chemotherapy may have an adverse effect on survival was not borne out by multifactorial analysis. Others have found a definite benefit from this modality of therapy (1,17). The lack of benefit might be explained by the time period of the study, in which: more advanced multiagent anthracycline-based chemotherapy was not used; there may have been a selection bias in choosing patients to receive chemotherapy; and there may have been a selection bias in the criteria used to include patients as receiving chemotherapy. The authors did not make any attempt to decide whether or not therapy was adequate, and any patient who received any therapy, whether single or multiple agent within the first two months, was accepted as having received chemotherapy.

The distribution of lymphomas was different in this series compared to other large series such as that of Azab et al (3) and Lewin et al (5). Thirty-seven per cent of the present cases were stomach, compared to 36% and 56% in the other series, respectively; 39% small bowel, compared to 34% and 36% in the other two series, respectively; and finally, 24% large bowel compared to 7% and 9%, respectively. However, in these other cited series, ileocecal lymphomas were classified separately. Four of the present large bowel lymphomas were cecal, and if one removes these from the present group, large bowel lymphomas represent 17% of the group, probably not very different from what others report.

In summary gastrointestinal non-Hodgkin's lymphoma does not appear to have a particular set of symptoms that would alert a clinician to the possible diagnosis. The authors' analysis followed the same survival curve as did

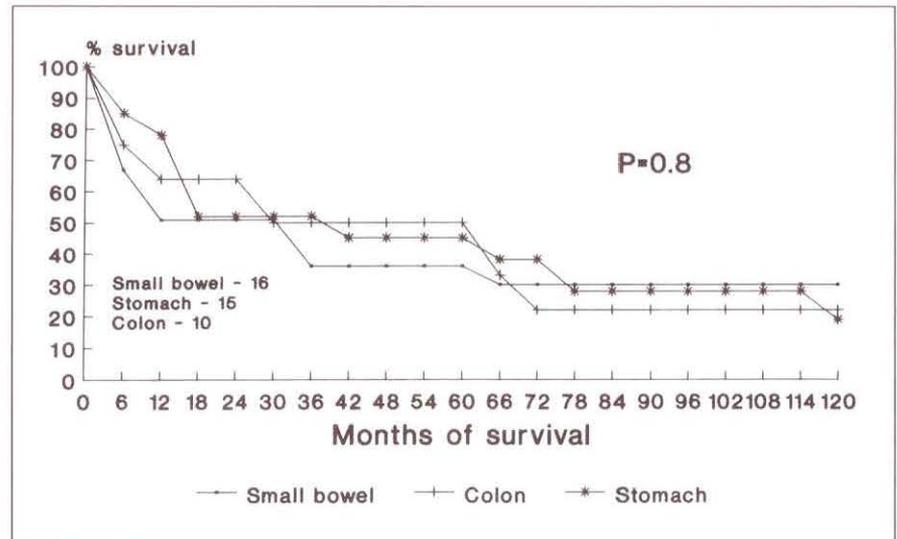


Figure 6) Actuarial survival plots of patients with gastrointestinal lymphomas depending on site of disease

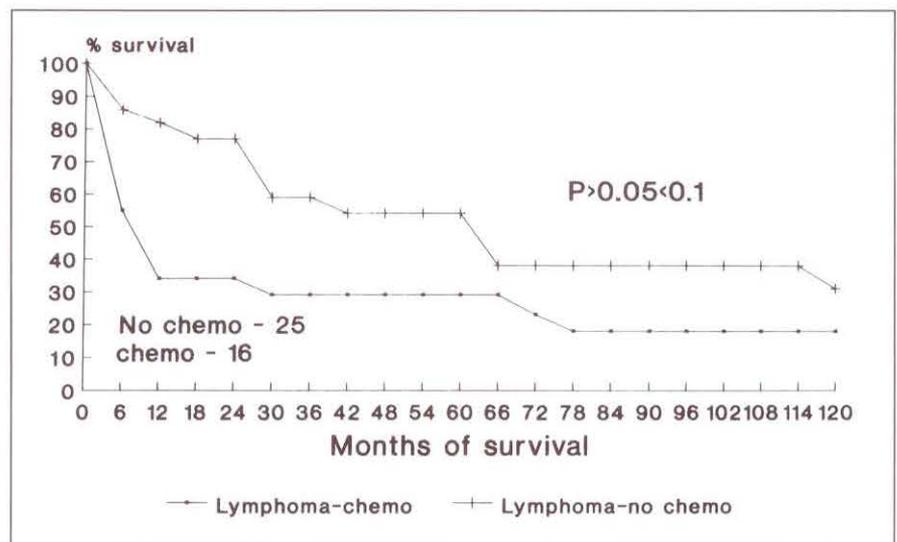


Figure 7) Actuarial survival plots of patients with gastrointestinal lymphomas depending on whether they had initial chemotherapy

their review of all lymphomas in the same time period, but a few differences seem noteworthy. Female sex is an independent predictor of survival, which was not found in the authors' analysis of the entire group of non-Hodgkin's lymphoma (4). Stage was also not found to be a factor, and although this has been found by others (2,15), the authors may have influenced this by excluding stage IV patients. They did not have a large group of 'good prognosis' patients, so histology as a factor could not be properly assessed. Most importantly, the same type of survival curve was seen with this group as with the entire group,

so that it would seem reasonable to apply the same principles of therapy to this group of lymphomas as are used for nongastrointestinal non-Hodgkin's lymphoma. Resection, if possible, may still be indicated, although perforation can occur in resected individuals, from unrecognized areas.

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