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PRIMARY GASTROINTESTINAL LYMPHOMA: A CLINICOPATHOLOGICAL STUDY OF 58 CASES

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Background. **Primary non Hodgkin's lymphoma (NHL) of the gastrointestinal tract (GI) is the most frequent extranodal lymphoma accounting for approximately 40% of all extranodal primary NHL. The role of surgery and other treatment modalities in the management of these patients is still controversial.**

Patients and Methods. **We reviewed the records of 68 patients with primary GI-NHL. Ten patients had incomplete records and were excluded from further evaluation. The records of 58 patients were considered, and all were available for analysis and follow-up.**

Results. **The most frequent site of involvement was the stomach (47 patients), followed by ileum (7 patients), large bowel (3 patients) and duodenum (1 patient). Malignant lymphomas of follicular center cell origin represented the most prevalent histologic types, accounting for 58% (34 of 58) of all cases. Stage, evaluated according to the criteria of Musshoff, was I_e in 15 cases, II_e in 16, III_e in 7, and IV in the remaining 20 cases. The median survival for the entire group of 58 patients was 54 months, with 46% of patients surviving at 5 years. The median survival was 71 months for patients in stage I-II, 60 for patients in stage III, and 25 for patients in stage IV ($p = 0.016$). Moreover, we found significantly improved survival in patients undergoing surgical tumor resection ($p = 0.003$).**

Conclusions. **Even if at the present time the optimal management of primary GI-NHL is difficult to assess, our data suggest that it is prudent to advise resection followed by adjuvant CT in most patients, whereas CT alone should be considered only when surgery cannot be performed.**

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Primary non Hodgkin's lymphoma (NHL) of the gastrointestinal tract (GI) is the most frequent extranodal lymphoma, accounting for approximately 40% of all extranodal primary NHL [1-3]. The most common site of presentation is the stomach, followed by the small intestine (particularly the ileo-cecal region in young adults), the colon-rectum and the lower esophagus [4].

Until the 1960's radical surgical resection represented the initial treatment, as it was for other gastrointestinal tumors, basically because a preoperative diagnosis of lymphoma was seldom performed [5].

However, in recent years the diagnosis of GI-NHL has almost always been made by endoscopic biopsy [3] or, as in gastric lymphoma, by cytologic examination of brushings of the tumor obtained with the fiberoptic gastroscope [5]. The development of these diagnostic procedures and the availability of a preoperative diagnosis of lymphoma have determined important changes in the management of primary GI-NHL.

On the basis of retrospective studies, some authors [6-10] have suggested that surgery should be considered cautiously since it is diagnostic in only a few cases, and radio and/or chemotherapy may be similarly effective in resected or unresected patients, with minimal risk of perforation and bleeding, thus avoiding postoperative complications.

On the other hand, several authors [11 12] have reported that radical surgical resection, in combination with splenectomy and hepatic and lymph node biopsies, provides the opportunity for a more precise staging, which is necessary for tailoring treatment based on the extent of the disease. Moreover surgery by itself may be curative for patients in stage I [13-16].

We report here the results of a retrospective analysis of 58 patients affected by primary GI-NHL and referred to our Institution over a period of two decades, with the aim of contributing to a clarification

of the role of surgery and other treatment modalities in the management of these patients.

Materials and methods

The records of 738 patients admitted to our Institution for NHL between January 1, 1969 and December 31, 1990 were reviewed to identify cases of primary GI-NHL. According to the criteria stated by Hermann et al. [6] and Lewin et al. [17], we defined as affected by primary GI-NHL only patients having malignant lymphoma involving the GI tract, with symptoms referable to this lesion at the time of the initial presentation. Patients who did not comply with these criteria were excluded from analysis. Out of 121 patients who had GI lymphoma involvement, we found 68 cases with primary GI-NHL. Ten patients had incomplete records and were excluded from further evaluation. The records of the remaining 58 were considered, and all were available for analysis and follow-up.

All pathologic specimens were re-evaluated according to the Kiel classification [18] and Working Formulation [19].

Patients were completely staged and classified according to the Ann Arbor system [20], modified for extranodal lymphoma as suggested by Musshoff [12]. Routine staging procedures included a complete history and physical examination, complete blood count with differential, biochemical profile, chest radiographs, and more recently, bone marrow trephine biopsy and computed tomography.

Surgery was performed in 46 patients. Twenty-three patients underwent laparatomy before the histologic diagnosis was available. An additional 23 patients were submitted to laparotomy after the diagnosis of NHL was established by endoscopic biopsy. Seventeen patients underwent partial gastrectomy, 10 patients total gastrectomy, 10 total gastrectomy plus splenectomy, and 9 were treated by segmental resection of the involved area.

Initial treatment. Eleven patients were treated by surgery alone, 32 by surgery and chemotherapy (CT), 2 by surgery and radiotherapy (RT); 10 patients received CT alone, 2 CT and RT, 1 patient underwent surgery and thereafter was treated with CT and RT. Chemotherapy was administered in 45 patients (77%) and represented the prevailing therapeutic approach after surgery. The combination of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) [21] was used as the predominant chemotherapeutic regimen; it was administered to 14 patients for a total of six to eight cycles. Thirteen patients received chemotherapy according to the COP regimen [22], 7 according to MOPP [23], 3 according to COP-BLAM [24], 3 according to MACOP-B [25], 2 according to ProMACE-CytaBOM [26] and 1 according to CNOP [27]. One patient was treated with Chlorambucil alone, and one with Chlorambucil plus α-interferon. Radiotherapy (30 Gy) to the stomach-bed and upper abdomen was performed in 5 patients with primary gastric lymphoma.

All data were collected and analyzed with the Statistical Package for Social Sciences (SPSS) [28]. Survival curves have been calculated with the life-table method [29], and the differences between groups assessed by the log-rank test [30]

Table 1. - *Clinicopathologic Features of 58 patients with primary GI-NHL*

Feature	n cases = 58
Sex	
male	34 (59%)
female	24 (41%)
Mean Age (yrs.)	56.72
range	12-82
Stage	
Ie	15 (26%)
IIe	16 (28%)
IIIe	7 (12%)
IV	20 (34%)
Systemic Symptoms	
A	36 (62%)
B	22 (38%)
Bulky Abdominal Disease	12 (21%)
present	12 (21%)
absent	32 (55%)
not reported	14 (24%)
Site	
stomach	47 (81%)
small bowe	8 (14%)
colon-rectum	3 (5%)

Results

Patient characteristics are summarized in Table 1. Out of 16 patients in stage II_E, 14 were in Musshoff's stage II_2 (87%), while only two cases were in stage II_1 (13%).

At onset the most frequent site of involvement was the stomach (47 patients), followed by the ileum (7 patients), large bowel (3 patients) and duodenum (1 patient).

Fourteen patients had gastric lesions confined to the middle third, 12 patients to the antrum and 3 to the cardias region. The tumor occupied almost the entire stomach in the remaining 19 patients.

Histologic subtypes defined according to the Kiel classification and Working Formulation are listed in Table 2. Malignant lymphomas of follicular center cell origin represented the most prevalent histological types, accounting for 59% of all cases (34 out of 58). Two cases were classified as «lymphoma of mucosa associated lymphoid tissue» (MALT) [31 32]. Intermediate- or high-grade lymphomas, according to the Working Formulation, accounted for 85% of cases.

The macroscopic features of the GI lesions are listed in Table 3. Three main patterns could be recognized. Large superficial or penetrating ulcers were the characteristic findings in 17 patients (16 gastric and 1 colon-rectum NHL); diffuse infiltration with large rigid, sometimes giant, folds occurred in 12 patients

Table 2. - *Histologic subtypes diagnosed in 58 patients with primary GI-NHL*

Kiel classification	Working Formulation										
	A	B	C	D	E	F	G	H	I	J	unclassified
Lymphocytic	5										
Centrocytic		1	1								
Centroblastic-centrocytic				5	2	18					
Centroblastic							7				
Immunoblastic								12			
Lymphoblastic									2		
Lymphoepithelioid											
Histiocytic											
unclassified											3
"Malt"	2										

Table 3. - *Macroscopic Findings and Diagnostic Modalities in 58 patients with primary GI-NHL*

Feature	Stage				
	Ie	IIe	IIIe	IV	total
Main pattern					
ulceration	6	5	4	2	17
diffuse infilatration	3	4	1	4	12
polypoid	3	2	2		7
not classified	3	5		14	22
Size of primary lesions					
<5 cm	7	4	4	2	17
>5 cm	3	7	3	6	19
not reported	5	5		12	22
Diagnosis on:					
endoscopic biopsies	11	10	5	10	36
resection material	4	6	2	10	22

(5 gastric, 5 ileal and 2 colon-rectum NHL); polypoid tumor mass was found in 7 patients (5 gastric and 2 ileal NHL). However, sufficient information on the macroscopic findings of primary lesions was not available in 22 patients. Therapy varied widely during the period considered, mostly depending on the extension of the disease and the diagnostic modalities. Table 4 outlines the clinical outcome, as related to stage and treatment modalities.

At last follow-up (December 31, 1990) 32 patients were alive, with a median follow-up of 46 months (range 3-151). Twenty-six patients died, 1-62 months after diagnosis. We did not record post-operative complications or surgery related deaths.

The median survival for the entire group of 58 patients was 54 months, with 46% of patients surviving at 7 years. Nine out of 35 patients in CR relapsed 5-37 months (mean 15 months) after completing initial therapy, with an estimated 5-year freedom from relapse of 66.8%.

Table 4. - *Clinical outcome related to stage and treatment modality in 58 patients with GI-NHL.*

Stage	Therapy	CR	PR	NR	Relapse
Ie	resected				
	- no further therapy	6			1
	- CT/RT	8			3
	unresected				
	- CT	1			1
IIe	resected				
	- no further therapy	3			1
	- CT	9	2	1	1
	unresected				
	- CT			1	
IIIe	resected				
	- CT	3		1	1
	unresected				
	- CT		1	2	
IVe	resected				
	- no further therapy	1		1	
	- CT	3	4	4	1
	unresected				
	- CT	1	1	3	
	- CT + RT		1	1	

Overall survival and freedom from relapse are shown in Figure 1. The extent of the disease proved statistically significant as a prognostic factor because of the difference in survival rates among the different stages ($p = 0.016$). The median survival was 71 months for patients in stage I-II, 60 months for patients in stage III and 25 months for those in stage IV.

No differences in survival rates were observed when comparing sex, histologic subtype, systemic symptoms, presence of abdominal bulky lesion at on-

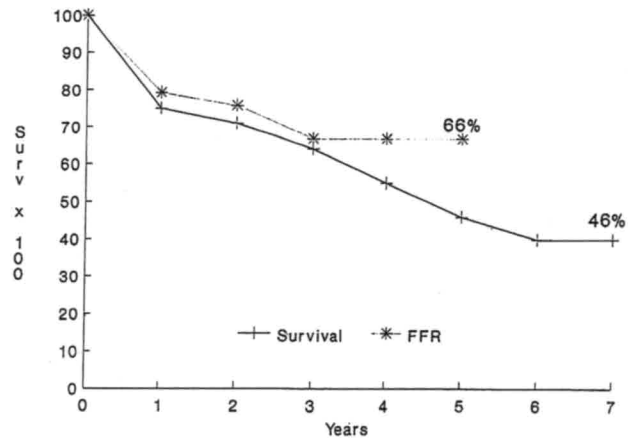

Fig. 1. - Overall Survival and Freedom From Relapse (FFR) in 58 patients with primary GI-NHL.

set, primary site of tumor or macroscopic features (Table 5). Most of these results might be explained by the small size of different subgroups and by changes in the therapeutical approach over time.

Table 5. - *Estimates of Survival Probability by Pronostic Factors in 58 patients with primary GI-NHL.*

Characteristics	No. of Patients	5 Year-survival (%)	P value
Overall	58	46	
Sex			
Male	34	56	0.724
Female	24	35	
Stage			
I	15	72	0.014
II	16	66	
III	7	57	
IV	20	17	
Histology			
Low grade	7	54	0.675
Intermediate grade	32	35	
High grade	14	58	
Symptoms			
A	36	56	0.197
B	22	35	
Bulky disease			
Present	12	58	0.255
Absent	32	49	
Macroscopic features			
Ulceration	17	68	0.673
Polypoid	7	42	
Diffuse infiltration	12	45	
Size of lesions			
<5 cm	17	61	0.165
>5 cm	19	53	
Surgical approach			
Gastrectomy	37	50	0.003
Bowel resection	9	76	
No surgery	12	25	

Patients diagnosed as affected by GI-NHL after 1984 had a median survival of 62.8 months, whereas those diagnosed before 1985 had a median survival of 32.1 months ($p = 0.03$). However, more patients had stage IV in the former than in the latter period (63% vs 20%). This finding, in addition to the larger number of patients undergoing surgery in recent years, could explain the differences in survival rates.

In our analysis the leading determinant of long-term survival was found to be the therapeutic approach. We recorded significantly improved survival ($p = 0.003$) in patients who had surgical tumor resection. We even noted a better prognosis in the subgroup of patients with gastric lymphoma treated with surgical resection (5-year survival of 50% vs 20%; $p = 0.0005$).

Discussion

Recently, the diagnosis of GI-NHL has been increasing, in particular gastric lymphomas [33]. This is probably due more to greater diagnostic accuracy than to a real rise in incidence.

Until several years ago most Authors supported the idea that surgery represented the first therapeutic step for these patients [13-15 34-38]. Since endoscopic biopsies were rarely available, this widely accepted opinion was based on experience of diagnosis known only after, rarely before, surgical resection. Besides, radical surgical resection seemed to be curative in stage Ie patients [13-16]. Surgery was preferred for several claimed advantages: a) more accurate staging; b) abatement of the risks of life-threatening hemorrhage and/or perforation related to infiltration of the GI wall, more frequent in unresected patients treated by CT/RT; c) possibility of removing bulky lesions and thus enhancing the probability of success of subsequent treatments [10].

Moreover, surgery has an irreplaceable diagnostic role since lymphoma grows in the submucosa and invades the mucosa only late in its course [8]. Surgery seems to be very important because of its ability to discriminate accurately among stage I_e, II_{e1} and II_{e2} according to Musshoff, even if nowadays some Authors emphasize that the involvement of non contiguous lymph nodes, a condition addressing the diagnosis of stage II_{e2}, can now be recognized by noninvasive procedures such as bipedal lymphangiography or Computed Tomography [40].

Lately, even de-bulking appears to be overcome. Shiu et al., Economopoulos et al., and Danova et al. reported long survivors and CRs after CT+RT among unresectable patients affected by large tumor burden [5 39 41]. On the other hand, our experience with these patients supports removing bulky lesions. Out of 12 patients affected by bulky abdominal lesions, we recorded 85% CR (6/7) and 15% PR (1/7) after surgery followed by CT, whereas in the group of 5 unresected patients we observed no CR, 40% PR, with the remaining 60% of cases undergoing a rapid progression of the disease.

Even if only about 65% of patients can be resected and some authors emphasize the high mortality related to surgery [3], our analysis does not demonstrate deaths related to perioperative complications. On the other hand, we recorded 3 deaths related to toxicity resulting from CT.

Gobbi et al. reported no differences in surivival rates between patients with gastric lymphoma treated with surgery plus CT and/or RT, and patients treated with CT alone, suggesting the uselessness of surgery in the therapeutical approach to these pa-

tients [40]. The present study, on the contrary, does not confirm this opinion because of the great difference in survival found between resected and unresected patients. Moreover we recorded a high number of NR's after chemotherapy in unresected patients (7/12), independent of stage.

There are conflicting reports in the literature concerning the importance of the histologic classification in the determination of long-term survival [42]. Analyses containing sufficient numbers of patients to allow comparison of subgroups have usually been collected over 20-30 years and span a wide variety of treatments [42]. Lewin et al., Gospodarowiczs et al. reported that prognosis appeared to correlate best with the stage of disease, rather than the histologic subtype [17 36]. However, Dragosics et al., who classified tumors according to the Working Formulation and the Kiel, Lukes and Collins, and Rappaport classifications, found that survival was significantly affected by histology: the higher the grade the poorer the prognosis [16]. The present study, where an analysis of the relevance of histology was performed on the basis of the Working Formulation, did not find a significant difference in survival among groups of patients with low, intermediate and high-grade GI-NHL.

However, since the majority of patients (85%) had an intermediate or high-grade lymphoma, it may be difficult to detect differences in this small series.

As in other series [5 35 36 38 43], in the present study tumor size and histology do not hold prognostic significance in patients undergoing radical surgical resection.

It is difficult to assess the true contribution to long-term survival of adjuvant therapies after radical surgery in GI-NHL, since randomized studies are not available. Shiu et al. and Weingrad et al. reported significantly improved survival for patients with gastric involvement who received either CT or RT after surgery [5 14]. The usefulness of adjuvant therapy after surgery has been supported by Shimm et al. and Bellesi et al., who reported that most recurrences were distant from the primary sites of lesion [44 45]. There have also been several suggestions that CT may be a more adequate treatment than RT alone after surgery, even in patients with limited disease [42 44 46]. Indeed Di Marco et al. recently reported that a clear difference in survival rate did not emerge between patients treated or not treated with postoperative chemotherapy [47]. Like Bellesi et al. [45], we noted successful responses in stage Ie and IIe patients treated with CT after surgery. Nowadays CT is performed in patients with unresectable disease or advanced stage lymphoma, in limited stage, and in patients submitted to partial surgical resection. Moreover, new trends in the treatment of GI-NHL suggest that patients should be given more aggressive regimens [3 9 42], although Sheridan et al. reported that the utilization of schemes containing anthracyclines is not necessary in patients who received CT after surgery [46]. We observed more favorable results after the use of schemes containing anthracyclines, although the results might have been conditioned by treatment modalities changing through years.

At the present time optimal management appears to be too far away to be identified, because of the infrequent occurrence of primary GI-NHL and the conflicting results of several reports. Therefore, we think that careful prospective randomized trials will be necessary to determine the best therapeutic approach to this disease. Until such predictive information becomes available, we believe it is prudent to advise resection in patients who are medically fit to undergo surgery. In addition, primarily on the basis of our experience, we think that CT after surgery is necessary in most cases, while CT alone should be considered only in selected cases, when surgery cannot be performed.

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