The role of surgery in the treatment of gastrointestinal lymphomas other than low-grade MALT lymphomas

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ABSTRACT

Background and Objectives. **A bias in clinical investigations on gastrointestinal lymphomas is the lack of testing the intention to treat as to resection, emergency conditions at presentation and selection brought about by the evaluation of feasibility of surgery.**

Design and Methods. **A prospective study involved 154 patients with gastrointestinal nodular or high-grade MALT lymphomas, 111 with a gastric and 43 with an intestinal presentation. The decision to resect or treat conservatively was left to clinicians, on condition that it was previously defined for each patient.**

Results. **Failure-free survival was significantly higher in the 106 resected patients than in the 48 unresected ones but did not differ according to either primary intention to treat or emergency surgery/elective treatment. Survival was similar in patients operated on by choice and in those because of an emergency. Intentionally unresected patients had a significantly better survival than those not undergoing surgery despite the initial intention, for a number of clinical reasons. Patients with gastric lymphoma survived longer than those with intestinal disease and prognostic factors were analyzed separately in the two groups. The best predictors of prognosis were performance status and serum lactic dehydrogenase level in gastric lymphomas, resection alone in intestinal ones.**

Interpretations and Conclusions. **The prognosis of gastric lymphomas depends on lymphoma-related factors and not on surgical treatment. The prognosis of intestinal ones is exclusively related to surgery. These data support the appropriateness of different clinical approaches to gastric and intestinal lymphomas.**
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Key words: gastric lymphoma, intestinal lymphoma, prognosis, therapy

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Controversies surround the clinical approach to primary gastrointestinal lymphomas (PGL) and problems remain concerning their therapeutic management. The increasing possibility of endoscopic biopsies, allowing pre-operative diagnosis in most patients, has so far failed to define the exact therapeutic value of surgical resection, separate from this latter's diagnostic role.[1-3] The identification of lymphomas deriving from mucosa-associated lymphoid tissue (MALT)[4,5] with particular biological and clinical behaviors has further differentiated and multiplied therapeutic possibilities, while introducing other problems concerning the true effectiveness and correct timing of the new treatments.[6] Conflicting results have been yielded from studies investigating the most important clinical factors that should guide treatment: extent of disease,[7] size of local tumor,[8] involvement of local or regional lymph nodes,[9] depth of digestive wall invasion,[10] and histologic features[11] have been separately indicated as the most important factors. The biases that often recur in such studies are retrospectiveness and/or variable selection of patients (with inclusion limited to patients either with early stage disease, or who have had their disease successfully resected or those with involvement of only a section of the gastrointestinal tract). The variable component of low-grade MALT lymphomas in these series is very attractive for investigators and readers, because of the many interesting aspects regarding epidemiology, histopathology, cancer modelling, and modulation of clonal cell population. However, the problems of clinical management of primary gastrointestinal lymphomas are not exhausted by low-grade MALT lymphoma which represent only 24–50% of this group of diseases.[12,13]

In 1990 the *Gruppo Italiano di Studio dei Linfomi* (GISL) started a prospective study with the main purpose of testing the actual, specific, therapeutic value of surgical resection. Since the associated centers did not reach an agreement on a uniform treatment strategy regarding surgical and conservative options, it was considered acceptable for the aim of the study that the decision to resect or not was left to each

institution on condition that it were previously defined and reported. A secondary aim of the study was to investigate the clinical factors which affect the patients' prognosis most significantly.

Design and Methods

From January 1990 to June 1997 the GISL Centers observed and treated 154 patients who fulfilled Lewin's criteria[14] for diagnosing PGL; presenting gastrointestinal signs and symptoms and prevalent – though not exclusive – lymphomatous lesions of the digestive tract. No exclusion criteria (age, comorbidity, etc.) were previously fixed in order to avoid any patient selection prior to the evaluation of surgical operability, that had to be an important conclusive judgement after the staging procedures. Table 1 illustrates the patients' main characteristics.

Disease staging was investigated according to the requirements of the Cotswolds Meeting.[15] In particular, staging workup included radiologic and/or endoscopic examination with multiple biopsies of the upper or lower gastrointestinal tract, and computed tomography of the thorax and abdomen. Endoscopic ultrasound was carried out in 10 patients. Patients were staged according to Musshoff's categories.[16]

Pathologists were called on to revise the histologic assessment of all cases of their own center and to submit equivocal specimens to external pathologists; 41 cases underwent such intercenter re-evaluation.

Low-grade MALT lymphomas were excluded from this study because of their favorable biological and clinical characteristics[5] and mainly because of their ability to respond to antibiotic therapy[17] and even to be definitively cured by surgery alone in cases of unifocal presentation.[18] High-grade MALT lymphomas, including cases with variable co-existing low- and high-grade MALT components, were considered as nodular lymphomas for the purposes of this study, since they have a worse prognosis than low-grade MALT lymphomas,[19] probably because of the observed lack of response of the high-grade component to antibiotics.[20]

Apart from cases requiring emergency surgery, the clinical approach towards nodular and high-grade MALT lymphomas, as far as concerned primary resection or preservation of the involved gastrointestinal tract, was left to the decision and experience of each participating center and/or clinician. Preliminary information had to be provided by each clinician about the surgical emergency level of each patient's presentation (life threatening, risk of major complications, comorbidity, etc.) and the conservative or surgical policy adopted in non-emergency conditions.

Treatment was differentiated according to histology until June 1994; thus 8 patients with small cell, lymphocytic or lymphoplasmacytoid lymphoma were treated with intermittent chlorambucil, 2 patients with follicular small cleaved cell lymphoma received BACOP[21] multiple drug therapy, while subjects with histologic types in the intermediate- or high-grade group of the Working Formulation received Pro-MECE-CytaBOM (65 patients) or MACOP-B chemotherapy[22] (16 patients). After June 1994 the Group decided that PGLs should receive a uniform chemotherapy regimen irrespective of histology because of

the prevalent specific needs of the gastrointestinal presentation over those of different histologic subtypes in terms of manageability and uniformity of administration intervals: thus a CHOP variant (CNOP[23]) was chosen in which mitoxantrone (12 mg/m²) substituted adriamycin (50 mg/m²). This regimen was administered to 63 patients.

Radiotherapy was optionally given only when residual tumor masses seemed to persist at restaging after primary therapy or when bulky masses were present at onset. In these cases only the involved field was irradiated with a total dose ranging from 28 to 38 Gy.

Complete remission (CR) was defined as complete regression of measured lesions and disappearance of any other objective evidence of lymphoma for at least 3 months. Partial remission (PR) consisted of a decrease of more than 50% in the sum of the products of the diameters of the measurable lesions. No response (NR) was anything less than a 50% decrease in measurable lesions. According to the Cotswolds Meeting recommendations for extramediastinal masses, gastrointestinal lesions were evaluated as bulky when their largest diameter was greater than 10 cm.

For the purposes of this work the failure-free survival (FFS) was considered the most appropriate event/time parameter, since it computes time from the start of treatment to any one of the following events: death from any cause, disease progression during treatment, no CR at the end of treatment, relapse. In this way, it is a better reflection of true effectiveness of a clinical approach than overall survival, which may not record the lack of success of a first line treatment when an effective salvage therapy is available.[24]

Many clinical features were scrutinized to evaluate their individual role in discriminating FFS. The Kaplan and Meier estimate[25] was used in univariate analysis for qualitative variables, whereas a simple linear regression applied to the proportional hazard model was used for quantitative parameters.[26] A multiple regression analysis was also performed, within the same proportional hazard model,[26] to select the best clinical features related to FFS.

Results

Figure 1 shows a comparison of the FFS of the 106 patients who were surgically resected with that of the 48 cases in whom surgery was not a first step in their clinical management. On the whole, the clinical response of resected cases seems better than that of unresected ones. One peri-operative death was recorded among operated cases, a 49-year old man with an intestinal large cell, anaplastic lymphoma who had severe intestinal bleeding 9 days after surgery and who died despite a second operation. The only recorded major complication after surgery was intestinal obstruction from multiple perivascular inflammatory adhesions which required further surgery. On the other hand, among non-resected patients a 55-year old patient with gastric large cell lymphoma (immunoblastic type) died of massive sudden gastric bleeding during chemotherapy. Another man aged 39 with a Burkitt-like intestinal lymphoma had intestinal perforation after 4 cycles of chemotherapy to which he was

Table 1. Clinical characteristics of the patients studied.

Characteristics	Gastric		Intestinal		All	
	No.	%	No.	%	No.	%
Total	111	100	43	100	154	100
Sex						
Male	71	64.0	30	70.0	101	65.6
Female	40	36.0	13	30.0	53	34.4
Age (years)						
15 - 29	3	2.7	1	2.3	4	2.6
30 - 39	5	4.5	5	11.6	10	6.5
40 - 49	17	15.3	13	30.2	30	19.5
50 - 59	28	25.2	10	23.3	0	24.7
60 - 69	42	37.9	10	23.3	52	33.8
70 - 79	15	13.5	4	9.3	19	12.3
80 - 85	1	0.9	0	0.0	1	0.6
Histology						
Small lymphocytic/lymphoplasmocytoid	6	5.4	2	4.7	8	5.2
Follicular, small cleaved cell	1	0.9	1	2.3	2	1.3
Diffuse, small cleaved cell	2	1.8	2	4.7	4	2.6
Diffuse, mixed small and large cell	21	18.9	5	11.5	26	16.9
Diffuse, large cell	43	38.7	13	30.2	56	36.4
Diffuse, large cell immunoblastic	13	11.8	10	23.2	23	14.9
Lymphoblastic	5	4.5	2	4.7	7	4.5
Small non cleaved	0	0.0	2	4.7	2	1.3
Anaplastic, large cell	4	3.6	2	4.7	6	3.9
High-grade MALT	16	14.4	4	9.3	20	13.0
Stage (Musshoff's categories)						
I	24	21.6	4	9.3	28	18.2
II$_1$	15	13.5	4	9.3	19	12.4
II$_2$	14	12.6	12	27.9	26	16.9
III	13	11.8	2	4.7	15	9.7
IV (including digestive multifocality)	45	40.5	21	48.8	66	42.8
Bulky mass	26	23.4	19	44.2	45	29.2
Systemic symptoms						
absent (A)	63	56.8	24	55.8	87	56.5
present (B)	48	43.2	19	44.2	67	43.5
"B" for fever and/or night sweats	10	9.0	2	4.7	12	7.8
Performance status						
100-90	43	38.7	9	20.9	52	33.8
80-70	52	46.9	26	60.4	78	50.6
60-50	14	12.6	6	14.0	20	13.0
40-20	2	1.8	2	4.7	4	2.6
Surgery						
resected	71	64.0	35	81.4	106	68.8
unresected	40	36.0	8	18.6	48	31.2

	Mean±1 SD (range)	Mean±1 SD (range)	Mean±1 SD (range)
Erythrocyte sedimentation rate (mm at first hr.)	29.3±25.6 (2-110)	34.4±26.5 (3-101)	30.7±25.7 (2-110)
Hemoglobin (g/dL)	12.5±2.0 (5.9-17.0)	11.2±2.1 (4.8-16.5)	12.1±2.1 (4.8-17.0)
Serum lactic dehydrogenase (U/L)	408±356 (116-2626)	333±205 (114-1252)	397±324 (114-2626)
Serum albumin (g/dL)	3.75±0.61 (2.10-5.00)	3.61±0.70 (1.60-4.90)	3.71±0.64 (1.60-5.00)

No statistically significant differences were noted in the distribution of the tabulated clinical characteristics between patients with gastric or intestinal presentation.

poorly responding; he had to be operated upon. Second line chemotherapy was then administered with no response and the patient died of his disease 10 months after diagnosis and 7 after surgery.

No differences became evident in relation to the types of chemotherapy used, nor to the addition of radiotherapy after chemotherapy, which was performed in 12 patients.
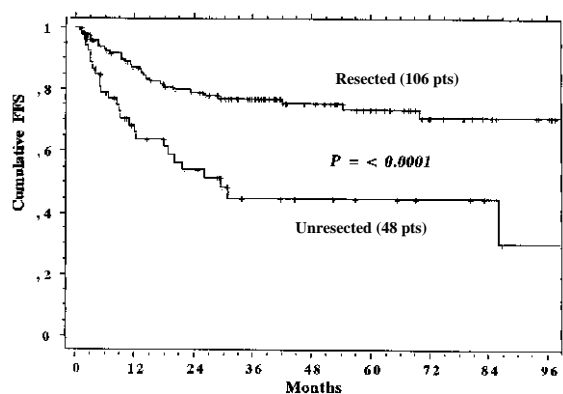
Figure 1. Failure-free survival of patients with gastric or intestinal lymphomas. The comparison is between 106 surgically resected and 48 unresected cases.
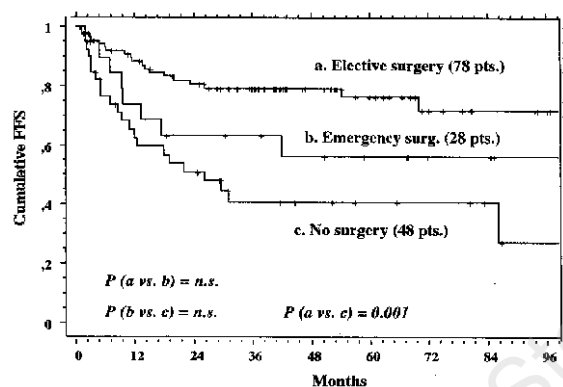

Figure 2. Failure-free survival of patients with gastric or intestinal lymphomas. Comparison between 28 patients who underwent emergency surgery, 78 who were operated upon electively and 48 who were not operated on.
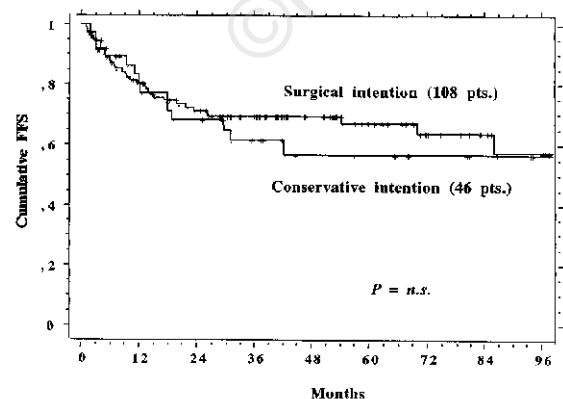

Figure 3. Failure-free survival of patients with gastric or intestinal lymphomas according to intention to treat by gastrointestinal resection. One hundred and eight were intended to undergo surgery, 46 to be treated conservatively.
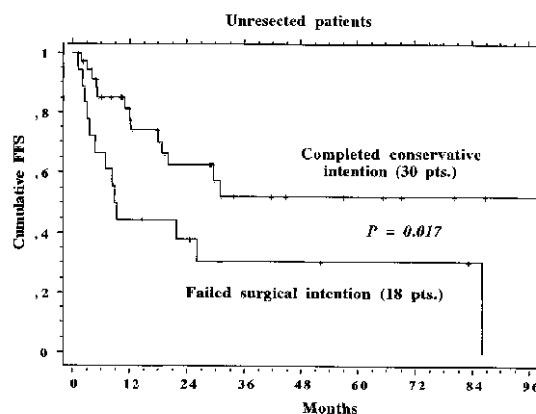

Figure 4. Comparison of failure-free survival within the group of 48 unresected patients. Clinicians intended conservative treatment for 30 of them, in the remaining 18 the original surgical program was not feasible because of inoperability.

Emergency surgery at onset was required in 28 patients, 12 with gastric and 16 with intestinal presentation, because of conditions which were evaluated by the clinicians as being directly life-threatening or having too high a risk of major complications with conservative therapy. These conditions can be summarized in partial or complete bowel obstruction (14 patients), severe active gastrointestinal bleeding (10 cases) and painful and large, clinically unmanageable, ulcerative lesions (4 subjects). Figure 2 shows that the FFS of these 28 patients was not significantly different from that of the 78 who underwent elective surgery whose FFS was decidedly better than that of the 48 who were not operated at all.

Figure 3 demonstrates that in the overall study population there were no differences in FFS in relation to the clinician's primary intention to treat with or without surgery. However, in the group of the 48 patients not operated upon (Figure 4), the prognosis was significantly different between those in whom the conservative program was actually carried out (30 patients) and the 18 who, despite being identified as potential candidates for surgery were not operated upon: this happened because of either extreme abdominal diffusion with multiple visceral involvement (7 cases), or bulk excess (7), or too high an anesthesiologic risk (4) due to heavy comorbidity, advanced age, or poor general conditions. In contrast, in the group of 106 operated patients illustrated in Figure 5 the prognosis was not different in the 90 who were programmed for surgical resection and in the 16 who, in spite of an initial intention to treat conservatively, had to be operated upon because of emergency situations or major complications at diagnosis.

A first univariate analysis on the whole population of 154 patients was carried out to select clinical factors that might most probably be related to prognosis. Table 2 summarizes the results of this first screening.

The result of this univariate analysis regarding gastric or intestinal presentation, together with some clinical observations, led us to perform the subsequent mandatory step of multivariate analysis separating
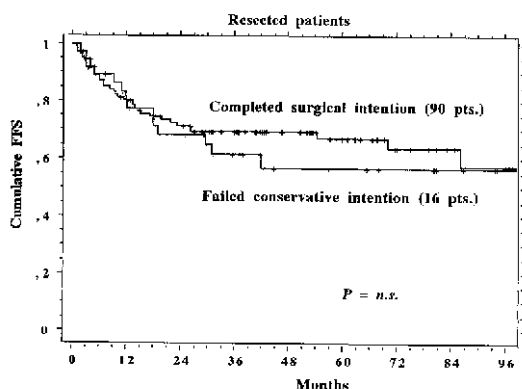
Figure 5. Failure-free survival in the 106 resected patients. In 90 surgical resection was the intended treatment and was carried out, in the remaining 16 patients the intended treatment was conservative but emergency conditions intervened requiring surgery.
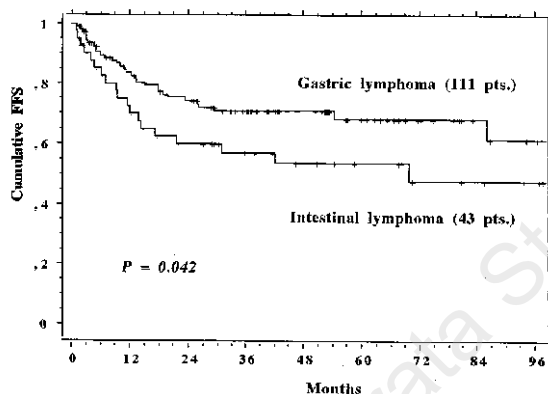

Figure 6. Comparison of the failure-free survival of 111 patients with gastric lymphomas and of 43 others with intestinal lymphomas.

Table 2. List of the clinical variables analyzed with the univariate technique in relation to FFS in 154 primary gastrointestinal lymphomas with histology other than low-grade MALT lymphoma.

Clinical variables	p value
Sex	.6556
Age	.1755
Site of presentation (gastric vs. intestinal)	.0411
Histology (low- vs. intermediate- vs. high-grade)	.3998
Stage (5 Musshoff's categories)	.0799
Systemic symptoms (A or B)	.4346
Bulky disease (at least 1 Ø > 10 cm or otherwise)	.5916
Performance status (Karnofsky index)	.0236
Erythrocyte sedimentation rate (mm at 1st hour)	.9751
Hemoglobin (g/dL)	.7406
Serum albumin (g/dL)	.4556
Lactic dehydrogenase (mU/mL)	.0076
Surgical resection (yes vs no)	.0078

Table 3. Clinical characteristics significantly related to FFS, separately in gastric and in intestinal lymphomas, nodular plus high-grade MALT type. Results of multivariate analysis with a proportional hazard model. Covariates entering the study were the best ones (i.e., with $p < 0.1$) emerging from univariate analysis (see Table 2).

Gastric lymphoma	*all stages* (111 pts.)	*I-II2* (53 pts.)
Clinical covariates	p	p
Performance status	< 0.0001	0.0056
Lactic dehydrogenase	0.0003	0.0484
All the others	> 0.1	> 0.1

Intestinal lymphoma (43 pts.)	
Clinical covariates	p
Resection (yes/no)	0.0011
All the others	> 0.1

gastric from intestinal lymphomas. As a matter of fact, patients with intestinal lymphoma generally fare worse (Figure 6) than those with a gastric presentation, have a lower prevalence of both good performance levels (Karnofsky index ≥ 90: 21% vs. 39%) and early stages (I+II1: 18% vs. 35%), and present with bulky tumor with a higher frequency (44% vs. 23%). However, no differences were found in the distribution of the main prognostic factors (stage, histology, age, bulky masses, lactic dehydrogenase) between patients admitted to either a conservative or surgical policy, both in the group with a gastric presentation and in that with an intestinal presentation.

Table 3 reports the results of the proportional hazard multiple regression analysis performed separately in gastric and in intestinal lymphomas utilizing all the clinical factors indicated as potentially important in the previous univariate study. In the gastric group only performance status and serum lactic dehydrogenase level demonstrated a statistically significant correlation with FFS, even considering all stages cumulated and the early stage subset separately, while surgical resection was the only statistically significant prognostic parameter in the patient group with an intestinal presentation. This should mean that the apparently important role of surgery, emerging from univariate analysis of the whole population with gastrointestinal lymphoma, may be substantial only in the subset of patients with an intestinal presentation, while in those with gastric primary involvement the currently adopted decision criteria for surgical resection cover more important clinical factors which actually have a stronger influence on prognosis.

Discussion

The consequence of choosing a rather extensive definition of PGL, like Lewin's one,[14] is that advanced stages are also included in the study population. From a general point of view, the restriction of analyses to early stage disease is very popular among PGL investigators, mainly because it is considered a guarantee of true primary onset of the lymphoma from the gastrointestinal tract. However, the search for such a guarantee should be strictly justified when exploring the relationship of a lymphoma with epidemiologic, environmental or dietary factors. Selection of only early stages for clinical trials is currently widely accepted but limits the general validity of the results of such trials, since the treatment of advanced stage PGLs may not necessarily be extrapolated from the experience related to early stage patients. One can expect that an early stage lymphoma has a higher probability of response to localized treatment measures than advanced stage disease. In contrast, as far as the value of surgical resection in the treatment policy is concerned (debulking, reduction of the risk of perforation or hemorrhage related to treatment), clinical information from advanced stages must be considered homogeneous to that from early stages, since both stages share risks and consequences regarding the management of bulky tumor, gastrointestinal wall bleeding and/or perforation. From this point of view, there seem to be no reasons why stage III and IV patients (many of whom are stage IV due to multifocal gastrointestinal involvement) have to be discharged because of the uncertainty about the primary site of onset when dealing with therapeutic problems of gastrointestinal wall localization (bulky mass, perforation or bleeding during chemotherapy).

The old and still unresolved controversy about the true clinical role of tumor resection in the overall treatment program for patients with gastrointestinal lymphomas might benefit from some new evidence.

Gastric and intestinal lymphomas show rather different clinical behaviors. Several authors have already emphasized this concept either through survival curve analysis[1,27,28] or by reports of a higher risk of complications for the intestinal presentation.[29] Amer and Akkad,[30] like us, found that intestinal lymphomas have a more unfavorable clinical presentation at diagnosis (advanced stages, B symptoms and, in the present series, also more bulky tumor and less favorable performance status) than gastric lymphomas. This difference does not seem to be related to a possibly more difficult or delayed diagnosis, since the median duration of signs and/or symptoms before diagnosis in gastric and intestinal lymphomas was 6.1 and 5.1 months in Amer and Akkad's series and 3.1 and 3.0 in the patients of this study, respectively. Thus, only an intrinsically higher biological aggressiveness can be postulated for intestinal lymphomas. For all these reasons it seems appropriate that future studies give separate results for gastric and intestinal lymphomas, rather than deal with indistinct *gastrointestinal* presentations. The very different results for gastric and intestinal lymphomas found in the multivariate analysis performed in this study further confirm this need and strengthen such advice.

As a matter of fact, considering the intention to treat with or without surgery proved to be a potential clue to explain the differences between the conclusions of a number of studies. Like the GISL study, the *German Multicenter Study Group on GI-NHL*[1] also left the decision to resect surgically or not to each associated center. This is a strategy that allows a co-operative group to collect and study patients differently treated according to a few available choices in a definite protocol, on condition that the decision in each case is previously defined and formally transmitted by the clinician to the monitoring trial office, and any other prognostic factor can be reasonably considered under control in the study. However, the German Group did not exploit this information thoroughly and analyzed patients only according to resections actually carried out instead of also taking into account the original intention for surgery. The present demonstration (Figure 4) that patients who cannot be operated upon – in spite of a systematic intention to operate whenever possible – do much worse than those who are not resected within a conservative policy, may seem entirely likely – and even expectable – but did not receive attention in previous studies. It is probable that any comparison between resected and unresected PGL patients is potentially affected by such a negative selection for subjects who would benefit from surgery according to the clinician's preset criteria, but who are unable to undergo such surgery because of a variety of reasons which are prognostically adverse (severe comorbidity, anesthesiologic risks, heavy bulky mass, multiple visceral infiltration). Resection, with the preceding unavoidable evaluation of feasibility, works as a selective factor and in studies which compare survival in resected and unresected patients such a bias must be considered the greater, the more invasive the policy adopted. Under this point of view, the demonstration that lactic dehydrogenase and performance status are the main prognostic factors in gastric lymphomas, just overcoming the importance of surgery, appears to be logically explanable. In fact, the former is one of the best indices of tumor growth and invasive potential in non-Hodgkin's lymphomas;[31] the latter reflects both the impact of the disease on the organism and the body's response to the tumor[31] and, moreover, is commonly considered in the evaluation of a patient's operability. Thus, it does not seem surprising that in gastric lymphomas these two parameters play a predominant role over all the others considered.

The corresponding comparison (Figure 5), among resected patients, of those managed according to a surgically oriented clinical policy with those coming from an intentionally conservative approach, but operated upon because of true emergency or high risk conditions, failed to demonstrate any survival difference. This comparison involved only very few cases of intestinal lymphoma. This might simply mean that the possible emergencies (presented mainly by gastric lymphomas) are easily and successfully managed in the available national health organization, but intrinsically confirms that the ultimate prognosis of gastric lymphomas is related more to its clinical presentation than to effective resection. In other words, surgery

Table 4. Comparison of literature data on gastric lymphoma series between peri-operative mortality (during operation and/or in the following 30 days) in resected patients and non-resection-related major complications in unresected ones (i.e. perforation or gastric bleeding which were cause of death or required emergency surgery).

Reference	Year	Resected patients	Peri-operative deaths	Un-resected patients	Non-resection-related major complications
Orlando et al.[35]	1982	24	4	NG	NG
Paulson et al.[36]	1983	36	3	0	0
Shimm et al.[37]	1983	25	0	NG	NG
Jaubert et al.[38]	1985	4	0	3	0
Farello et al.[39]	1987	9	2	NG	NG
Domergue et al.[40]	1988	11	0	4	1
Taal et al.[41]	1989	33	0	41	2
Manfé et al.[42]	1989	8	0	2	0
Azab et al.[9]	1989	37	1	0	0
Gobbi et al.[34]*	1990	682	49	188	5
Rossini et al.[43]	1990	23	0	12	0
Maor et al.[32]	1990	0	0	34	2
Chirletti et al.[44]	1991	17	2	0	0
Aviles et al.[33]	1991	24	1	28	0
Mosca et al.[45]	1991	11	0	0	0
Blazquez et al.[46]	1992	1	0	15	0
Morton et al.[47]	1993	48	1	28	3
Valicenti et al.[48]	1993	44	3	33	3
Pasini et al.[49]	1994	53	0	0	0
Rigacci et al.[50]	1994	66	3	0	0
Montalban et al.[19]	1995	103	5	28	3
Haim et al.[51]	1995	0	0	24	3
Zinzani et al.[29]	1995	82	0	0	0
Koch et al.[1]	1997	58	0	64	0
Takenaka et al.[2]	1997	25	0	0	0
Tondini et al.[52]	1997	0	0	17	0
Sano et al.[53]	1997	50	0	0	0
Gobbi et al. (present series)	1999	78	0	33	1
Total		1,609	75 (4.7%)	587	27 (4.6%)

*Review of 19 references from 1973 to 1988. NG = Not given.

seems to be needed only when a complicated presentation of lymphoma occurs, but even after the necessary cure of the potentially fatal complication the prognosis is still linked to the characteristics of the tumor and to the relationship between host and tumor.

We just mention that some investigators[32,33] feel that the risk of gastric perforation or severe bleeding during chemotherapy or radiotherapy in unresected patients has been overestimated and one of us[34] – through an incomplete literature review made in 1990 – has already suggested that this risk could be considered as, at least, comparable with that of peri-operative mortality in resected patients (which includes deaths occurring during surgery and in the 30 days after). An update of this review (Table 4) substantially confirms these conclusions. Moreover, apart from the mere comparison of mortality and/or

life-threatening complications, a somewhat different quality of life can be hypothesized for the two groups of surviving patients, i.e. those whose stomach has been partially or completely resected and those whose stomach has been preserved.

According to our data, bulky mass should not be included among prognostically important features. Some doubts on the true prognostic significance of bulky tumor have already been raised,[54,55] since its supposed significance was noted to be derived from studies on systematically resected patients. Now, we know that a frequent reason why a surgeon does not perform a gastrectomy is an excess of tumor bulk or, which is nearly the same, too wide an infiltration of contiguous viscera. It is not clear why in a number of preceding works tumor bulk was considered important, and debulking mandatory, only when surgery was feasible, disregarding the fact that patients who are inoperable because their masses were too large, in spite of a putatively less favorable prognosis, actually retain a discrete possibility of cure. Thus, it seems reasonable and justified that when unresected patients are also taken into account, bulky mass is no longer important as a prognostic factor.

On the whole, the results from gastric lymphomas support the idea that prognosis of these patients is not affected by initial surgery, not even when it is unavoidable for emergency conditions, but is mostly influenced by very common and simple clinical parameters – performance status and lactic dehydrogenase – which mainly depend on lymphoma aggressiveness and host reaction. As long as the risk related to surgery (especially if a total gastrectomy is needed) is comparable with that of perforation and hemorrhage related to conservative management, both treatment policies are strictly justified, even though the probable (but here not demonstrated) better quality of life of the unresected patients might weigh in favor of a conservative option. Thus, in gastric lymphomas surgery should be strictly limited to possible emergencies at presentation, and can be avoided in the large majority of cases.

Intestinal lymphomas yielded different results, with tumor resection being the unique significant prognostic factor, as recently pointed out by Zinzani et al.[56] This probably has a number of reasons. First of all, in intestinal lymphomas surgery still retains an important and largely unavoidable diagnostic role, thus the number of unresected patients tends to be low anyhow. Endoscopic biopsies are possible only in the duodenum and in the large intestine; unfortunately, the majority (59%) of the intestinal presentations involve the jejunum and ileum, and the cecum, a site which can be endoscopically biopsied only with some difficulty, is primarily involved in another 11% of patients. These patients must undergo laparotomy in order to make a diagnosis, and there are no available data advising against tumor resection after intraoperative diagnosis of lymphoma. Second, by virtue of these surgery-aided diagnostic requirements, it can be expected that there are proportionally fewer unresected cases in intestinal lymphomas than in gastric lymphomas, thus leaving too few cases for correct comparison. Third, the prevalence of large intestine involvement must be verified in a series of

unresected intestinal lymphomas, since according to some investigators[30] primary site colorectal lymphomas, with lesions which can be diagnosed from endoscopic biopsies and more easily offer the possibility of conservative treatment, seem to have an intrinsically poorer prognosis. In our 8 patients with unresected intestinal disease, 6 of whom are dead, 4 had lymphoma developing in the colon; this is a higher proportion than in resected patients. We do not know whether the higher concentration of colorectal presentations in patients with unresected intestinal disease might explain their worse prognosis. Severe hemorrhagic complications or perforation of the intestinal wall cannot account for the fate of our unresected patients, since only one case of bowel perforation occurred. This perforation happened in a 45-year old man who was not initially operated upon because of an enormous and quickly growing bulky tumor of the ileum; chemotherapy was preferred to a very complex and mutilating operation. The patient achieved a 16-month complete remission then relapsed and died of resistant and progressive disease.

In conclusion, the small number of observed patients with intestinal lymphoma makes the results regarding this presentation worth verifying in a larger population. Intestinal lymphomas seem to have a more severe presentation than their gastric counterparts, and it has not been clarified whether the poorer prognosis of unresected patients is related to the omission of surgery in the treatment sequence or other associated unfavorable factors in these subjects. In the meantime, contrary to the advice for their gastric counterparts, it appears appropriate and cautious to resect intestinal lymphomas whenever possible.

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Potential Implications for clinical practice

◆ This work demonstrates that in gastric lymphoma surgery should be strictly limited to possible emergencies at presentation and, therefore, can be avoided in the large majority of cases. In contrast, intestinal lymphomas require surgical resected whenever possible.