

Designing clinical trials on gastric lymphomas and reporting outcomes

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The correct treatment of gastric lymphoma (GL) is a very controversial topic of modern oncology. Until 10-15 years ago surgery played a crucial and undisputed role, being the first and mandatory treatment because of its intrinsic and irreplaceable diagnostic value. Now GLs are generally diagnosed through endoscopic examination and so not only has the diagnostic value of gastrectomy but also its distinct therapeutic role become comparable with those of any other treatment option, such as radiation therapy and chemotherapy, alone or combined. A huge number of conflicting reports have accumulated about the optimal indications for and the best efficacy of the available therapeutic tools, particularly of gastric resection compared to conservative treatments, and so the issue remains debated. Several reviews¹⁻³ illustrate these different opinions very well.

Understanding why such different conclusions on the role of gastric surgery in GL have actually been drawn and published may help clarify which investigational biases give rise to such scattered results and should therefore be avoided in the future. Thus, we shall focus here on some methodologic requirements of GL clinical management and research that, on the one hand, can account for the variety of conclusions reached so far and, on the other hand, should offer a guideline for correct planning of clinical trials and interpretation of results.

In particular, we urge that a few and homogeneous criteria be defined and fulfilled when dealing with GL patients. Such criteria should form the basic requirements strictly necessary to the quality of reports and the logical background of the research, and thus to the reliability of results and the relevance of conclusions. These points will be discussed here.

Definition, primitivity and staging

One of the most important preliminary statements regards what we actually mean by *gastric lymphoma*, since many different definitions have

been used. With reference to the general case of lesions possibly involving any section of the digestive tract, according to Dawson *et al.*⁴ a lymphoma can be defined as gastrointestinal when spread to contiguous lymph nodes alone may be associated with the digestive lesion, but concomitant involvement of other non-contiguous lymph nodes, or liver, spleen and bone marrow must be excluded. Moreover, even minimal peripheral leukemic expression must be excluded too. On the contrary, Hermann *et al.*⁵ and Levin *et al.*⁶ think that only patients with either predominant gastric/intestinal lesions or presenting symptoms due to digestive tract involvement can be considered as having a gastrointestinal lymphoma. Differently, according to D'Amore *et al.*,⁷ in the presence of both lymph nodal and gastrointestinal disease a lymphoma can be considered *gastrointestinal* when the cumulative extranodal lesions exceed 75% of the total tumor volume (or the lymph node component does not exceed 25%).

When dealing with lymphomas the undefined term *gastrointestinal* can generally be accepted only during staging investigation and with reference to the diagnostic criteria adopted, which are in fact the same for both gastric and intestinal lymphomas. However, an increasing amount of evidence demonstrates that intestinal lymphomas are very different from gastric ones with respect to presenting features, prognostic factors and response to therapy.⁸⁻¹¹ Thus, after diagnosis, independent of the definition chosen, any further management of gastric and intestinal lymphomas should follow distinct clinical protocols. Obviously, separate evaluation of results is highly recommended.

Especially for GLs, the definition chosen directly influences the selection of clinical stages in a study as does the reliable classification of the primary lesion being in the digestive tract. We will try to clarify the multiple interrelationships of these concepts. Obviously, the more restrictive the adopted GL definition, the higher the probability that only early-stage patients will be considered and thus their lymphomas evaluated as primary.

On the other hand, with a more extensive definition also advanced-stage patients would be considered but the strictly gastric primary nature of their lymphoma cannot be guaranteed, since late diffusion to the stomach from an originally involved lymph node may have occurred. From a general point of view we may wonder whether the present interest in primary site is fully justified. In fact, there is no similar prerequisite in the evaluation of the lymphomatous involvement of other organs except for purposes of anecdotal clinical reporting. Also, the guarantee of primary site has seldom lead to the discovery of peculiar clinical and biological features among lymphoma presentations. Broadly speaking, the primary site of GLs should be investigated in studies focusing on epidemiologic, environmental or dietary factors possibly related to the lymphoma genesis. But as for local response and gastric side-effects of the available treatments, early stages can be considered homogeneous to advanced ones, in that they share the risks of digestive-wall bleeding and/or perforation, bowel obstruction, severe diarrhea or consequences related to the management of bulky tumors. Of course, the overall clinical results will broadly differ between early and advanced stages, for example in terms of remission rate and duration, as well as survival,² as is generally observed and expected with lymphomatous presentation in any other body site.

Which staging system should be considered the most appropriate for GL remains debated. The poor applicability of the Ann Arbor criteria is generally acknowledged,³ since the most critical prognostic discrimination pertains to stage II, between involvement limited to local (paragastric) lymph nodes and spread to distant (mesenteric, retroperitoneal) ones. However, such a discrimination is permitted by several other classifications (Musshoff,¹² TNM,¹³ Blackledge,¹⁴ Lugano¹⁵). Since 1994, the Lugano staging system has been the most widely accepted and used.

Very likely, different patient selection and tumor staging according to the adopted GL definition directly influences patient outcome and the conclusions that can be drawn from clinical studies. A restrictive definition, resulting in the selection of greater numbers of early-stage patients, will naturally lead to assigning a great, and often prevailing, therapeutic role to locally active treatments, such as radiotherapy¹⁶ or surgical resection,^{17,18} whose impact on patient outcome can be expected to be clearly lower in a population selected with a more extensive definition.¹⁹

Why assessing primary site has become so popular in gastrointestinal lymphomas and what the actual value of the primary site in itself are interesting issues. The sneaking assumption that lymphomas with an extranodal origin could have specific and somehow different clinical features and course has long been found in clinical reports. Now we know that a primary extranodal lymphoma usually presents no particular clinical features, apart from the possible functional failure of the specific organ involved and a generally worse prognosis of the lymphoma in comparison with the nodal counterpart. This is an old and widely accepted observation and the number of extranodal sites involved is one of the five most important prognostic factors¹⁹ for non-Hodgkin's lymphomas. Thus, limiting studies to early-stage GL patients because of the unquestionable gastric origin of their disease seems to be a uselessly restrictive caution that is unusual for any other site of lymphomatous involvement. Indeed, in GL series, advanced-stage patients are frequently disregarded because there may be secondary involvement of the digestive tract. In theory, this choice would deny a priori even of the possibility of a truly gastric origin, with subsequent outside spread, for an advanced lymphoma of the stomach but since advanced GLs are nearly as numerous as early ones,²⁰ it is hard to accept on a logical ground that clinical and therapeutic experience can be inferred preferably, if not solely, from early cases. These issues have never been raised for any other extranodal site involved by a lymphoma (e.g., spleen, liver, kidney). Moreover, as far as gastrectomy is concerned, surgical resection has seldom been claimed as an important therapeutic step in any other lymphomatous presentation, independently of the primary site, because of the well-known sensitivity of lymphomas to chemotherapy and radiotherapy. Furthermore, if staging is important in differentiating therapy also in GLs, fairly accurate staging can be achieved with the currently available imaging techniques (mainly ultrasonographic endoscopy and computed tomography) as accepted for other types of lymphoma, and does not seem to justify surgical exploration of the abdomen.^{21,22}

MALT and "nodular" lymphomas

A reason why clinicians are preferably attracted to early GLs might be that they have learned that such presentations can be cured with surgery alone in a large number of cases and this observation has prompted them to improve clinical results through an increasingly accurate selection of truly early-

stage cases (*i.e.* the most likely primary ones). Evidence on the effectiveness of surgery in several patients accumulated over a long time before the advent of modern fiberoptic endoscopes, when the same surgical operation required for diagnostic purposes did actually achieve extensive and complete tumor resection under the reasonable suspicion of a carcinoma. The anatomical and clinical picture of a lymphoma patient in whom all evidence of disease has been removed by biopsy is a rather unusual one, when compared with any other presentation, and resembles *stage 0* in one the first lymphoma staging systems. Kaplan²³ defined *stage 0* as the clinical condition when no detectable disease is present after excisional biopsy. *Stage 0* was soon disregarded in the subsequent classifications and we have no information on the prognostic and therapeutic impact of such an early stage. Many localized GLs could certainly be allocated to this category and probably no other kind of theoretical *stage 0* patients could have received so complete a resection.

More recently, the identification of gastric MALT lymphomas, which likely arise as a response to local infective stimuli (*Helicobacter pylori*), grow slowly, respond to pharmacologic eradication of the bacterial infection and can spread outside the digestive tract or change into a high-grade lymphoma only late, has convinced investigators that the first, and so far the only, lymphoma with the unquestionable epidemiological, etiologic and clinical characteristics required by a true gastric primary is that originated from MALT. These concepts are now widely accepted, and the interrelationship and partial overlapping of the terms of MALT lymphomas, primary GLs and early GLs can explain prior emphasis on those clinical features that have been subsequently synthesized in the concept of MALT lymphoma (and, above all, in its good response to surgery). It is still debated whether any other type of GL can develop from a MALT, like high-grade MALT GL is recognized as the probable evolution of a low-grade one.²² Certainly, further insights into the process of histologic and clinical transformation could come from a systematic application of the criteria proposed by De Jong *et al.*²¹ to the pathologic evaluation of gastric biopsy specimens. These authors distinguished four histologic groups of MALT lymphoma, each with a different prognosis. The groups are: a) pure low-grade MALT lymphoma; b) low-grade MALT lymphoma with a minor high-grade component; c) high-grade MALT lymphoma with a minor low-grade component (blastic cells exceeding 10%); and d) high-grade MALT lymphoma, with only diffuse blastic

cells, without a low-grade component. The first histologic class seems to be the only one with a truly favorable prognosis, while the increasing blastic component in the remaining three leads to significantly lower overall and disease-free survival.

The nosologic identification of MALT lymphomas, especially with the particular biological and clinical behavior that characterizes the lower-grade types, has been a very attractive issue because of many interesting features regarding epidemiology, histopathology, cancer modeling and pharmacologic modulation of a clonal cell population. Though some aspects of their management are still to be defined, such as duration of response to antibiotics and ionic pump inhibitors, length of endoscopic follow-up, and timing and scheduling of anticancer drugs in case of failure, low-grade MALT GLs require a distinct clinical and therapeutic approach,²⁴ while it is accepted that high-grade MALT GLs must be treated as nodular ones.

Clearly, however, MALT lymphomas do not represent the whole of gastric lymphomas, but only 24 to 52%, according to several histopathologic reviews.²⁵⁻²⁷ A study including only stage I or II gastric lymphomas for the sake of primary origin obviously collects a higher proportion of MALT lymphomas, which unquestionably originate in the stomach and respond very well to low-impact and local therapies. Among the 197 patients reviewed by Brincker *et al.*²⁸ low grade MALT GLs formed 39% of the stage-IE -IIE subset but only 15% of the stage IIE-III-IV population.

Thus, the basic clinical and therapeutic differentiation must be between low-grade and high-grade MALT plus nodular GLs. We now know that many of the GLs cases identified based on primary site and early-stage presentation are actually low-grade MALT lymphomas. However, the distinction of low- from high-grade MALT and nodular lymphomas has become popular only lately, while variable numbers of unrecognized MALT lymphomas from recent series still exert direct and confusing influence on prognosis and treatment in the contemporary scientific literature.

Selection biases

Variable numbers of surgically resected GL patients are often not included and evaluated in literature series since not all of them are transferred from peripheral centers to reference institutions, mainly because of (peri-)operative mortality or too severe morbidity. Further selection may be made in the reference centers according to the inclusion or exclusion criteria of specific treatment

protocols and little or no information is generally given about the excluded patients. Obviously, even in centers oriented to perform gastric resection whenever possible, not all potential candidates for gastrectomy will actually undergo it. In these cases patients are excluded because of excessive anesthesiologic risk (due to heavy comorbidity, poor general condition, advanced age), or presurgical assessment of massive abdominal spread or tumor bulk. These cases should be singled out and listed separately both when reporting surgical GL series and also, for the opposite reason, when evaluating patients who have been treated conservatively. Unfortunately, this is rarely done. The excluded patients – in as much as not operated – generally have a very poor prognosis, as demonstrated by our group,¹¹ and much poorer one than those who fail to benefit from a conservative treatment program and are eventually operated on because of emergency complications. Thus, when evaluating the role of gastrectomy in the therapeutic planning of GLs, an analysis according to the intention to treat originally formulated for each single patient with respect to surgery should parallel the efficacy assessment of any treatment modality.

Time-dependent parameters

Finally, the statistical tools for the evaluating the clinical results must be chosen properly. Most literature studies use overall survival in their analyses. However, in a lymphomatous process, with its

well-known sensitivity to chemotherapy and radiation therapy, overall survival can miss what actually is the best front-line approach, due to the possible effectiveness of second- or third-line therapies. It is unlikely that overall survival by itself can be a convincing argument for or against the usefulness of staging gastrectomy, the early association of radiation therapy or other treatments included in the front-line approach. The available salvage therapies can be effective in rescuing failures and thus mask a sufficient number of failed front-line approaches.

Time to treatment failure (TTF), which considers time from registration into study to relapse, disease progression, treatment-related death or unjustified withdrawal, and freedom from progression (FFP), which calculates time from registration to progression or relapse, are better suited to take into account early failures. Overall survival, relapse-free, disease-free survival and remission duration should be considered useful complementary criteria but not the most important or the only ones in a statistical evaluation. It would probably be advisable to use overall survival only in general studies on GL prognosis, while TTF or FFP should be mandatory when evaluating the effectiveness of first-line treatment modalities. In a conservative approach, we can easily assess the correct choice also through *gastrectomy-free* survival which, furthermore, might be considered as an intrinsic estimator of life quality.²⁹

Table 1. Methodologic steps for designing a correct clinical protocol and evaluating results in GLs .

| Steps | Comments |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Choose the proper clinical definition | Restrictive, if you are investigating primary GLs or looking for epidemiological, environmental and dietary factors. (A restrictive definition will collect a higher number of low-grade MALT lymphomas, which will generally respond to local therapies and, likely, also to systemic therapies). Extensive, if you are investigating every other clinical matter (stratification by stage is needed when evaluating results). |
| Exclude intestinal lymphomas | They do worse, (this is true for both MALT and other than MALT lymphomas); surgery is mandatory |
| Select a definite histologic and clinical setting | Early stage, low-grade MALT lymphomas respond to antibiotics or gastrectomy; advanced-stage, low-grade MALT lymphomas respond to oral alkylating agents; high-grade MALT and "nodular" lymphomas need chemotherapy or combination therapy with or without surgical resection. |
| Control the intention to treat | This allows all the possible selection biases related to therapy to be either avoided or considered. |
| Use the correct time-dependent parameter | For general prognostic studies: overall survival. For first-line therapeutic modalities: TTF and/or FFP. For evaluation of gastrectomy consider <i>freedom from gastrectomy survival</i> . |

Summary and conclusions

The criteria we discussed can be arranged in a working order that should be followed when organizing clinical research on GL patients or reporting its results (see Table 1).

First of all, a basic preliminary step is to choose the most suitable clinical definition for GL according to an actual need to assess primary site and, especially, in relation to the investigational aims. The subsequent mandatory step is to distinguish gastric from intestinal lymphomas in terms of therapeutic management and evaluation of results, since their biological and clinical behavior and their response to therapy are very different.

Third, for clinical and investigational purposes a further crucial distinction must be made between low-grade MALT and high-grade MALT or nodular lymphomas, a biologically well-grounded differentiation that partially resumes and includes some of the reasons that currently justify the use of a restrictive GL definition, the selection of early-stage patients or the search for site of origin.

Fourth, it is important to define the disease stage setting in which we intend to evaluate the role and results of surgery, radiation therapy, and chemotherapy, alone or in combination. This is particularly true when dealing with GLs other than low-grade MALT. Such a criterion is substantially the same as for any other lymphoma presentation in which, however, advanced stages are studied at least as accurately as early ones. Information must be given on all the diagnosed patients, not only on treated ones, especially when focusing on the problems and results of gastrectomy. In this respect, evaluating clinical results relative to the original intention to treat seems to be a powerful and very convincing double-check.

Finally, the use of TTF or FFP, in addition to several other time-dependent variables, is recommended when first-line treatment is under evaluation.

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