Do current indications for surgery of primary gastric lymphoma exist?

J. C. Rodríguez-Sanjuán, R. A. García, S. Trugeda, F. de la Torre, J. Llorca1 and M. Gómez-Fleitas

Department of General Surgery II. Hospital Universitario Marqués de Valdecilla. 1Department of Prevention and Public Health. University of Cantabria. Santander, Spain

ABSTRACT

Objective: to analyze the results of our series in order to assess whether surgical excision is still a valid therapeutic option in case the patient needs surgery. Secondarily, to analyze Helicobacter pylori infection rate.

Patients and method: a retrospective study of 69 consecutive patients having stage I-Il primary gastric lymphoma; of these, 65 were treated by gastrectomy between 1974 and 1999. Mean age: 62.6 years (28-85). New staining of paraffin-embedded samples from the surgical specimen were carried out (hematoxiline-eosine, Giemsa, immunohistochemistry) and reviewed. The histological classification was performed according to Isaacson’s criteria. The statistical analysis was done by Chi-squared and Fisher’s exact tests, as well as Kaplan-Meier and Log-Rank tests.

Results: mortality was 9.2%. There were non-fatal complications in 10.8%. Helicobacter pylori was identified in 62.7%. Seven patients (11.9%) suffered a relapse. The 5-year survival probability was 87%. The statistical analysis did not show any influences of Ann Arbor stage, gastric wall invasion, Helicobacter pylori infection, histological type, or margin resection involvement on survival.

Conclusions: surgical excision provides a high rate of complete remissions and excellent long-term survival with acceptable mortality. Therefore it appears to be a valid treatment in case of emergency surgery, incidental finding, or lack of histological diagnosis.

Key words: Stomach lymphoma. Surgery.
clinical settings where surgery could be necessary. As a secondary aim, we analyzed the prevalence of *H. pylori* infection.

**METHODS**

We performed a retrospective study of 69 patients diagnosed as having primary gastric lymphoma according to Dawson’s criteria (16), in Ann Arbor stage I and II (17), between 1974 and 1999, who were treated by gastrectomy—with previous informed consent—at the time when surgery was considered the initial treatment of choice. The series consists of 36 women and 33 men with a mean age of 62.6 years (range: 28-85). Some of the patients were included in a previously published study (8).

In the first 15 patients of the series a diagnosis of gastric tumor was reached according to a barium upper gastrointestinal series. The diagnosis of GL was confirmed after histological analysis of the surgical specimen. In the remaining 54 patients, the diagnosis was done by gastroscopy and biopsy.

Staging was performed by physical exploration, peripheral blood study, chest X-ray, and bone marrow analysis in every case. In the earlier half of the series, the tumor was finally staged at celiotomy. After the introduction of computed tomography, it was used to stage the latest 23 cases. The stage was I in 59.4% and II in 39.1%.

A patient was also diagnosed as having acquired immunodeficiency syndrome, and was previously published (18). Treatment consisted of surgical excision in 65 (94.2%) and was non-surgical in 4-CT in 3 (4.3%) and *H. pylori* eradication in 1 (1.5%). Postoperative CT (consisting of CHOP) was given to 32 patients, and postoperative radiotherapy (RT) was added to 4. The study is focused on the 65 patients treated by gastrectomy. The tumor was located in the upper third in 4 patients, middle third in 27, and distal third in 30, and involved the entire stomach in 4. Partial gastrectomy was performed in 48 patients and total gastrectomy in 17, according to the distance to cardia criterion. Splenectomy was added in 7 cases due to tumor proximity, although with no spleen involvement in any of them.

Radicality was R0 in 50, R1 in 12 and R2 in 3. There was no residual tumor in 50 cases (R0). Extragastric invasion was found in 3 patients: jejunum in one case and mesocolon in two. In one of the latter, a segmental resection of colon was added, and in the other a residual tumor was left (R2). Microscopic margin involvement was found in 12 cases (R1). There were non-fatal complications in 7 patients (10.8%), and 6 died during the postoperative period (9.2%).

In 60 cases histology was revised with new stains (hematoxyline-eosine, Giemsa) of paraffin-embedded specimen blocks. The immunohistochemical study was performed by means of the soluble complex alkaline phosphatase-antiphosphatase (Biomed Corp., Foster City CA, USA). A prediluted panel (all from Cormedica, Spain) was used, the common leukocyte antigen CD 45 being a marker for lymphocyte cells, L26 a marker for B phenotypic lymphocytes, and UHCL1 a marker for T phenotypic lymphocytes.

Tumors were sorted according to Isaacson’s classification (19).

**RESULTS**

Fifty-one cases could be classified according to Isaacson’s classification: low-grade type B (LG) in 31 cases (61%), high-grade type B (HG) in 18 (35%), and type T in 2 (4%). Wall involvement could be assessed in 60 cases: total in 36 cases (60%) and partial in 24 (40%). *H. pylori* was identified in 32 of the 51 cases analyzed (62.7%). It was more common in LG tumors (63.3%) than in HG tumors (58.8%) (NS). Seven patients suffered from lymphoma recurrence (11.9%). The 5-year survival probability (SP) was 87.93% (Fig. 1). The statistical analysis (Table I) only found significant influence on PS for the Ann Arbor stage. No influence was shown for gastric wall invasion, *H. pylori* presence, margin involvement or Isaacson’s histological type, although the latter had a borderline statistical significance (p = 0.056). As a result, the hazard ratio by means of Cox regression was not estimated.
Patients with margin involvement and no other evidence of residual tumor did not show significantly poorer survival than patients having free borders. Although in positive-margin patients stage IIE was more common (26.7%) than in free-margin patients (16.7%), differences were not significant (Chi-squared = 0.6, 1 df, p = 0.4). No significant difference in tumor grade (13.3% of HG, 25% of LG) in positive margin patients (Chi-squared = 0.8; 1 df, p = 0.43) or in patients receiving postoperative CT (5%) of positive margin patients and 24% of free margin patients (Chi-squared = 0.2, 1 df, p = 0.6)-was seen either. Of note, all positive-margin patients who did not receive postoperative CT are alive, although one had a pulmonary recurrence after 20 months. As a result, excision radicality did not influence prognosis, and no survival significant difference was appreciated between R0 and R1 excisions.

**DISCUSSION**

Our experience analysis reveals, first of all, a good long-term survival (higher than 87% after 5 years), which can be considered an excellent oncologic result.

Second, no prognostic influence was found for any of the studied histological factors, including some with a reported value as border involvement or histological type. This finding is surprising, especially since in our previous study (8), with a shorter follow-up and fewer cases, we found a prognostic value for border involvement and histological type. This suggests a statistical effect, which could also change in a future analysis with longer follow-up or inclusion of new cases. However, other investigators found gastric wall involvement to be of prognostic value (10,13,15), although Koch et al. (20) found no prognostic influence for histological grade. The absence of any prognostic value in surgical margin involvement is surprising, although most patients (54.5%) did not receive additive CT or RT. As a result, radical excision (R0), according to the criteria used in carcinomas, was not associated with a significantly longer survival than excisions leaving microscopic residual tumor (R1). The small number of cases with macroscopic residual tumor (R2) precludes an assessment of influence. This study therefore does not support radical excision but only macroscopic tumor removal. In other works, excision without residual tumor has been associated with better long-term survival rates (10,12,15,21).

The classical indications of surgery for GL were diagnosis, staging, and treatment. Proper staging is presently achieved by means of computed tomography, endoscopic ultrasounds, and positron emission tomography (7), and therefore there is no longer a surgical indication. Although endoscopy has for a long time permitted diagnosis in most cases, a histological diagnosis cannot be achieved in some patients in spite of multiple biopsies. These cases will need a surgical procedure. It may be performed using a laparoscopic approach but a whole-thickness stomach biopsy is necessary, which would be more safely performed by means of an open procedure. It is possible that no additional surgery need be performed, and that the patient is treated with CT alone. However, our own data and those from other works (9-12) agree that surgical excision is still a good therapeutic option (Table II), with survival rates of 82 and 64% after 5 and 10 years, respectively, which is a comparable outcome to that of non-surgical treatment (7). However, although non-surgical therapy-related mortality rate is lower, and even nil in some series (5), it can be as high as 6% (3). Cases of bleeding or perforation—spontaneous or CT-induced—are less controversial since surgical excision is mandatory in most cases. It does not seem logical to perform a simple suture and then continue therapy if the tu-
The frequency of *H. pylori* in our series is in the reported range of 62-96% for LG and 52-79% for HG lymphomas (2), which is one of the main arguments in favor of its etiopathogenic relationship with MALT lymphoma. Although high lymphoma remission rates with eradication therapy alone have been reported (6,12,27,28), unresponsiveness is possible, especially if one or more of the following are present: HG histology (27), perigastric lymphadenopathy (28), tumor not confined to the mucosa (29) or presence of t(11;18)(q21;q21) translocation (26). Non-responders to eradication therapy usually respond to RT or CT, although another option is surgery (7,29).

Some aspects of molecular genetics with importance from a diagnostic and prognostic point of view are currently known. Three types of translocations are specifically associated with MALT lymphoma: t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18) (q32;q21). Other genetic alterations are also observed with different frequencies such as trisomies 3,12 and 18, p53 loss of heterozygosity/mutation, p15 and p16 promoter methylation, and fas gene mutation. (26). In GL, t(11;18)(q21;q21) is more frequently seen versus those confined to the stomach (26). These patients do not usually respond to *H. pylori* eradication therapy (26).

In conclusion, although we consider non-surgical therapy-CT-RT, *H. pylori* eradication-the treatment of choice, we think there are potential surgical indications such as absence of histological diagnosis, incidental findings, CT complications, or treatment failure. Surgeons must be aware that surgical treatment provides excellent long-term survival with a high local-control rate; therefore, they must have no doubts concerning the performance of gastrectomy in the above-mentioned circumstances.

**REFERENCES**