Information about mucosa-associated lymphoid tissue (MALT) has accumulated progressively over the past decade. MALT lymphoma is usually associated with a pre-existing disorder in sites where lymphocytes are not normally present and where an acquired MALT develops in response to either infectious conditions (i.e., in the stomach) or to autoimmune processes (i.e., in salivary glands or the thyroids). In the context of these prolonged, lymphoid-reactive proliferations, the outgrowth of a pathologic clone can progressively replace the normal lymphocytes (1,2). MALT lymphoma has been included in the Revised European–American Classification of Lymphoid neoplasms (R.E.A.L. classification) as a specific subtype, i.e., the extranodal marginal-zone B-cell lymphomas (R.E.A.L. classification) as a specific subtype, i.e., the extranodal marginal-zone B-cell lymphomas (3). Marginal-zone B-cell MALT lymphomas comprised 7.6% of more than 1400 non-Hodgkin’s lymphomas in a recent international evaluation of the clinical significance of the REAL classification (4).

Several lines of evidence, including sequence analysis of the immunoglobulin variable-region heavy-chain genes, strongly suggest that Helicobacter pylori provides the antigenic stimulus for sustaining the growth of MALT lymphomas in the stomach (5–7). This antigen-driven clonal expansion, which is mediated by mucosal T cells, may explain the tendency of low-grade MALT lymphomas to remain localized in the mucosal sites and to regress after H. pylori eradication (8,9). During this clonal expansion, genetic alterations continue to occur until a point is reached when autonomous (i.e., H. pylori-independent) growth is possible, while additional alterations can then result in high-grade transformation.

The principal histologic feature of low-grade MALT lymphomas is the presence of a variable number of lymphoepithelial lesions, resulting from the partial destruction of gastric glands by aggregates of small- to medium-sized neoplastic lymphocytes (10). Since early or borderline cases can be confused with H. pylori-related follicular gastritis, a scoring system has been devised to enhance diagnostic confidence (11).

Low-grade MALT lymphoma is usually a very indolent disease, often remaining localized for a prolonged period, with some cases showing no progression for several years even without treatment. There is increasing evidence that eradication of H. pylori can be the sole initial treatment when the disease is limited to the stomach, as is the case in at least 80% of the patients (11–14). However, it is still unknown whether treatment for H. pylori will avert relapse and, thereby, definitely cure at least some of the patients. Hence, long-term results of the initial studies are eagerly awaited. A first update of the German multicenter trial (13) is published in this issue of the Journal (15).

However, this report is only a modest addition to our knowledge about the duration of remission, since the median follow-up (2 years) is not much longer than that of other reports and in view of the very indolent course of this disease. Furthermore, it is unfortunate that the authors used neither the recently recommended staging criteria (16) nor the histlogic score proposed by Wotherspoon et al. (11), an omission that can impede comparison with other series.

However, in many respects, the report is a valuable contribution. First, it confirms the efficacy of antibiotics in inducing apparently durable lymphoma remission. Analogous data have been reported by our group and other groups, although, according to our experience, expecting a remission rate of greater than 80% in an unselected patient population appears overly optimistic. The efficacy of antibiotics, in fact, may be reduced in instances of locally advanced disease with bulky masses or deep infiltration of the gastric wall and in cases with increased numbers of scattered blast cells in the biopsy.

Second, Neubauer et al. (15) relate their observation that patients not responding to the eradication of H. pylori may harbor high-grade lesions, which initially were not or could not have been seen.

Finally, this report of a larger and thoroughly studied series supports the findings of Savio et al. (17) that polymerase chain reaction (PCR)-detectable B-cell monoclonality may often persist after the disappearance of histologically detectable MALT lymphoma. This result confirms not only that histologic examination remains the cornerstone of the management of this disease (17) but also that the significance of PCR-detectable monoclonality is questionable, since (at least as of now) the relapse rate does not seem to be influenced by this finding.

Where do we go from here? First, only a much longer follow-up can clarify the possible merits of H. pylori eradication. Nevertheless, we believe that this conservative approach as the sole initial treatment for localized disease should not be regarded as “still investigational,” as...
suggested by Neubauer et al., but is already advisable, provided that a strict oncohematologic and endoscopic follow-up is carried out.

Chemotherapy and local radiotherapy have been shown to induce complete remission in most patients and can, therefore, be used in individuals who do not respond to antibiotics (18,19). Surgery has been widely used in the past, with excellent results for localized disease. However, we strongly believe that the need for surgical resection in gastric MALT lymphomas should be redefined. Total gastrectomy, the only effective procedure in this multifocal disease (20,21), is a very aggressive treatment and does not prevent relapses outside the stomach. In the trial reported by Neubauer et al. (15), most patients who did not respond to the cure of H. pylori infection or who relapsed after antibiotics were referred for surgery. Seven patients were eventually treated in this manner, and two of them died (3 and 5.5 months after surgery) of unreported causes.

In a review of 93 patients from northern Italy (Brescia and Varese) and southern Switzerland (Bellinzona) (21), we found no statistically significant difference in either overall survival or event-free survival between patients who received different initial treatments (chemotherapy alone, surgery alone, surgery with chemotherapy or radiation therapy, or antibiotics against H. pylori). The actuarial 5-year overall survival is 82% (95% confidence interval = 67%–91%) in the series as a whole. At a median follow-up of 2 years, 10 of 93 patients have died, all but one of them of a second solid tumor. This unexpectedly high incidence of additional neoplasms was not treatment related and has meanwhile been confirmed in other series. The genetic instability, found in 50% of MALT lymphomas (22), may have a significant role in this disturbing unexplained finding.

Further elucidation will come from the ongoing European randomized trial investigating whether the addition of chemotherapy (chlorambucil) to the anti-H. pylori therapy is of any benefit in low-grade gastric MALT lymphomas.

With the growing popularity of stomach-conserving approaches, it will also become mandatory to evaluate prospectively the prognostic significance of the variable high-grade component in low-grade gastric MALT lymphomas (23). A further challenge will then be to define the molecular events responsible for the escape from H. pylori-mediated, antigen-dependent growth of low-grade gastric MALT lymphomas and the events that can cause transformation into high-grade lymphomas. The resulting information will be useful in choosing the appropriate therapeutic strategy for the individual patient.

Meanwhile, the study by Neubauer et al. and other studies have already confirmed the validity of the basic assumption of the REAL classification, i.e., that the various subtypes of lymphomas are distinct nosologic entities. They also add support to the assumption that, for all gastric lymphomas, initial surgery probably belongs to the history of medicine (24).

Moreover, it would not be surprising if, in the future, other anti-infection therapies (e.g., against hepatitis C virus?) could play a role in the treatment of lymphomas. Gastric MALT lymphoma really is more than just a fascinating model.

References


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Predicting Residual Disease and Local Recurrence in Patients With Ductal Carcinoma In Situ

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There is an old real estate joke that goes like this. Question: What are the three most important factors to consider when buying a house? Answer: ‘‘Location, location, location!’’

A form of this question might well be asked about patients with ductal carcinoma in situ (DCIS) of the breast. For example, what are the three most important factors for predicting local recurrence in patients with conservatively treated DCIS? Read on and I will give my answer.

The examination of serial tissue sections by Faverly et al. (1) and Holland et al. (2,3) revealed that DCIS is usually unicentric but commonly multifocal. In other words, it is generally confined to a single segment of the breast. It is often larger than expected, extending beyond mammographic microcalcifications, and skip areas (i.e., areas of DCIS with intervening normal breast epithelial tissue) are common. In spite of its extent, however, DCIS is a local disease, lacking the following two important components of the fully expressed malignant phenotype: invasion and metastasis. Therefore, complete excision will likely cure most patients. If complete excision cures the disease, how then does one accomplish this within the confines of obtaining an acceptable cosmetic result? Although there is no perfect tool, current data suggest that margin width is the best judge of complete excision.

In 1994, Faverly et al. (1) showed that 90% of DCIS lesions, regardless of their histologic type, were completely excised if all margins were 10 mm or more in dimension. Silverstein et al. reported in 1996 (4) and in 1997 (5) an 8% local recurrence rate for all conservatively treated DCIS lesions with margins of 10 mm or more. In 1997, Lagios and Silverstein (6) showed a 5% local recurrence rate at 84 months for conservatively treated patients with 10 mm or more margins, and the Nottingham Group (7) reported a 6% local recurrence rate among 48 patients with 10 mm or greater margins treated with excision only after a median follow-up of 58 months. These data clearly show the increasing importance given to wider margin width in the recent literature.

In this issue of the Journal, Cheng et al. (8) discuss the relationship between tumor size, margin status, and the probability of residual DCIS. I was particularly happy to read that most patients in their study had complete tissue processing with incising of all surfaces, serial sectioning of all tissue at 3-mm intervals, and three-dimensional reconstruction by the pathologist. It is only with this type of thorough, meticulous evaluation that size and margin status can be accurately assessed.

The relationship between tumor size, margin status, and the probability of residual DCIS is extremely important, since residual disease leads to most local recurrences. With this study, Cheng et al. indirectly corroborate our previous conclusions that size and margin status are independent predictors of local recurrence (4,5). Since most local recurrences are at or near the original lesion and are often a product of inadequate surgical removal of the primary lesion, resulting in residual disease, the conclusion drawn in the report by Cheng et al. makes perfect sense and further supports existing data.

I do, however, have a problem with some of the methodology used in their study. Cheng et al. (8) properly defined residual disease as “the persistence of DCIS in the re-excision and/or mastectomy specimens.” Therefore, for the determination of the presence of residual disease, each patient had to undergo an initial excision of the lesion followed by re-excision or mastectomy. Of the total of 232 patients, only 148 met these criteria and were evaluable for the presence of residual disease (90 patients subsequently treated with mastectomy and 58 subsequently treated with re-excision); 84 additional breast conservation patients had neither re-excision nor mastectomy (16 received radiation therapy following the original lumpectomy and 68 were treated with lumpectomy only), and, hence, they should not be included in the calculation of residual disease because their residual disease status is unknown.

When Cheng et al. state that only 28% of patients (66 of 232) had residual DCIS, they are underestimating the number of patients in whom DCIS was left behind. By including the 84 patients who had neither re-excision nor mastectomy as patients without residual DCIS, they dilute their results. The true estimate of residual disease should be derived from 66 patients with proven residual disease divided by 148, the number of patients who underwent re-excision or mastectomy and who were therefore evaluable for the presence of residual disease. By use of this calculation, the percentage of patients with residual DCIS is 45%, a number which matches more closely the one reported previously (9).

This methodology, using 232 patients as the number of evaluable patients, has been employed throughout the study, resulting in gastric lymphomas; pretreatment criteria and clinical relevance. Gastroenterology 1997;112:1466–74.


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