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Is endoscopic ultrasound clinically useful for follow-up of gastric lymphoma?

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Background: Endoscopic ultrasound (EUS) is considered the best technique for locoregional staging at diagnosis but its role in the follow-up of patients with gastric lymphoma after organ-conserving strategies has not been established.

Design and methods: We retrospectively evaluated 23 patients with primary gastric lymphoma treated with a stomach-conservative approach. Sixteen of them were affected by MALT lymphoma and seven by diffuse large-B-cell lymphoma (DLBCL). Five patients were treated with *Helicobacter pylori* (HP) eradication therapy alone (omeprazole + amoxicillin + clarithromycin); eight patients received a treatment including HP eradication and chemotherapy and the remaining 10 patients were treated with chemotherapy alone.

Results: At the end of treatment, a complete remission was documented in 21 (91%) patients by endoscopy with biopsy (E-Bx) but in only seven (30%) patients by EUS. A total of 99 evaluations with both EUS and E-Bx were evaluated and we found concordance between the two methods in 33 occasions (33%) only. No significant difference on the percentage of concordance was recorded between MALT and DLBCL. After a median follow-up of 36.5 months we have not observed any relapse in 12 patients (six DLBCL and six MALT) with a persistent positive EUS but negative E-Bx.

Conclusions: Although the length of follow-up cannot exclude late relapse, we think that in restaging and follow-up of gastric lymphoma, EUS seems not to be a reliable tool if it is abnormal and E-Bx still remains the gold standard. Therefore, after conventional conservative treatment, persistence of EUS abnormality with a negative histology should not be considered as a clinically relevant persistence of disease and should not be a reason for further treatment.

Key words: endoscopy, EUS, gastric, lymphoma

introduction

In gastric lymphomas, the rapid progress both in clinical management and biologic understanding of the pathogenesis has radically changed the approach to the disease [1]. Several studies have indicated that gastrectomy is no longer the first choice for gastric lymphomas and a stomach-conserving approach is now the golden standard [2–4]. The pathogenetic role of *Helicobacter pylorii* (HP) is a consolidated acquisition and several studies have confirmed that a simple antibiotic therapy (AT) for HP eradication is an effective treatment at least for low-grade lymphomas with limited disease [5–7]. In this perspective, an accurate staging system is necessary for the precise evaluation of the extension of disease and endoscopic ultrasound (EUS) has shown to be an useful tool for the definition of gastric wall involvement and for the detection of perigastric adenopathies, with a better accuracy than the combination of upper endoscopy, abdominal ultrasound and computed tomography (CT) scan. Several studies have confirmed the important role of EUS for locoregional staging of the disease and EUS is now included in the routine staging of gastric lymphomas. More importantly, EUS gives information for the prevision of response to HP eradication therapy since this therapy has shown to induce a high percentage of histological remission when the disease is confined to mucosa and submucosa [8–14]. Limited information is, however, available on the utility of EUS in the evaluation of response to treatment and subsequent follow-up. Early reports with small series indicated a role of EUS both for staging and follow-up [15]. A more recent report, however, has shown that endosonographic remission is documented with a significant delay when compared with the conventional histological remission [16]. We therefore conducted a retrospective study in our gastric lymphoma patients observed in the last 10 years, in order to compare EUS with conventional endoscopy with

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histology (E-Bx) for evaluation of disease during post-treatment follow-up.

materials and methods

From January 1994 to December 2003, a total of 51 patients with a diagnosis of gastric lymphoma were observed at our institution. Twenty-five patients were affected by diffuse large-B-cell lymphoma (DLBCL) and 26 by low-grade MALT gastric lymphoma (MALT). For the purpose of this study, only patients affected by localized gastric lymphoma treated with a stomach-conserving approach and with at least two EUS evaluations in the follow-up were selected. Therefore, a total of 28 patients were excluded from this analysis for the following reasons: 17 patients (12 DLBCL and 5 MALT) underwent partial or total gastrectomy, one had spread of disease beyond the stomach with supraclavicular adenopathies, one progressed and died during treatment, one died for second neoplasm without reaching an adequate follow-up, four were lost to follow-up before carrying out at least two EUS, one patient refused follow-up EUS and three patients underwent only one EUS during follow-up. The remaining 23 patients, representing the object of this study, had a median age of 60 years (range 26–79), 12 were male and 11 female (Table 1). Diagnosis was based on morphological and immunophenotypic analysis. Seven patients presented with DLBCL with or without residual areas of MALT while 16 patients were affected by MALT, two of them with focal sheets of large cells. HP infection was documented by urease test or by histology in all patients but one with MALT and in only one patient with DLBCL. All patients underwent staging procedures that included CT scan of thorax and abdomen, bone marrow biopsy and EUS. EUS staging was carried out according to TNM (tumour–node–metastasis) classification [17]. Extension of disease was defined according to the Lugano staging system [18] (Table 1). Five patients affected by MALT received AT alone for HP eradication (amoxicillin, clarythromycin and a proton pump inhibitor for 7–14 days). Eight patients affected by MALT were treated with HP eradication therapy followed by chemotherapy [monochemotherapy with chlorambucil or cyclophosphamide, or polychemotherapy with combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like regimens]. Ten patients, three MALT and seven DLBCL, were treated with chemotherapy alone and two of them, one MALT and one DLBCL, received radiotherapy of the stomach also at a dose of 30 Gy. Evaluation of response and subsequent follow-up was conducted with endoscopic biopsies (E-Bx) in any abnormal area and EUS at variable intervals according to clinical judgment. In the case of absence of suspected lesions, biopsies were taken randomly. Complete remission (CR) by E-Bx was defined as the disappearance of lymphoma findings at endoscopy and absence of histological lesions. Partial remission (PR) was defined as reduction of tumor at endoscopy or disappearance of tumor at endoscopy but persistence of lymphoma infiltrates on histological grounds. For MALT lymphoma the Wotherspoon score was used and patients with

Table 1. Clinical features, response to treatment and outcome of 23 patients affected by primary gastric lymphoma

Patient no.	Age	Sex	Histology	Lugano stage	HP	EUS stage	Therapy	Response (by E-Bx)	FU Months	Outcome
1	65	F	DLCL	II2	NE	T3N2	CHOP like	NR	44	LFU
2	42	M	DLCL	II1	POS	T3N2	CHOP	CR	71	CCR
3	59	M	DLCL	II2	NEG	T2N1	VACOP-B	PR → CR	48	Died without disease
4	64	M	DLCL	I	NE	T2N0	CHOP like	CR	58	CCR
5	34	F	DLCL	II2	NEG	T3N2	CHOP-R + RT	CR	37	CCR
6	79	M	DLCL	II1	NE	T3N1	CHOP like	CR	32	CCR
7	55	F	DLCL	II1	NEG	T4N2	VACOP-B	CR	25	CCR
8	26	M	MALT	I	POS	T2N0	AT + CHOP like	CR	120	CCR
9	66	F	MALT	IIE	NEG	T2N1	CHOP like + RT	CR	103	CCR
10	64	M	MALT	II1	POS	T3N1	CHOP like VACOP-B chlorambucil	NR/PR → CR → REL → PR	101	Alive in PR
11	43	F	MALT	I	POS	T2N0	AT + CTX	CR → REL	93	Alive in CR
12	50	M	MALT	I	POS	T1N0	AT + chlorambucil	PR → CR	80	CCR
13	62	M	MALT	II1	POS	T1N1	AT	NR → CR	32	Died without disease
14	78	M	MALT	I	POS	T2N0	AT	CR	50	Alive in CR
15	45	F	MALT	II1	POS	T2N1	AT + CTX/chlorambucil	CR	49	CCR
16	55	M	MALT	II1	POS	T1N1	AT	CR	36	CCR
17	41	M	MALT	I	POS	T1N0	AT + chlorambucil	CR	34	Alive in CR
18	65	F	MALT	II2	POS	T2N2	AT + CTX/chlorambucil	CR	29	CCR
19	69	F	MALT	II1	POS	T1N1	AT	CR	17	CCR
20	41	F	MALT	I	POS	T2N0	AT	PR → CR	11	CCR
21	75	M	MALT/DLCL	I	POS	T3N0	AT + CHOP like	CR	77	CCR
22	24	F	MALT/DLCL	I	POS	T1N0	AT + CHOP like	PR → CR	72	CCR
23	70	F	MALT	I	POS	T1N0	Chlorambucil	CR	108	CCR

AT, antibotic therapy; CCR, continous complete remission; CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; CHOP-R, CHOP plus Rituximab; CR, complete remission; CTX, cyclophosphamide; DCLC, diffuse large B-cell lymphoma; E-Bx, endoscopy with biopsy; EUS, endoscopic ultrasound; HP, *Helicobacter pylori*; LFU, lost to follow up; NE, not evaluated; NEG, negative; NR, no remission; POS, positive; PR, partial remission; REL, relapse; RT, radiotherapy; VACOP-B, combination chemotherapy with VP-16, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin.

a score ≤2 was considered as free of disease. At each EUS, the maximum thickness of the gastric wall was measured and endosonographic remission was defined as a wall thickness of ≤4 mm with a restoration of a normal layer pattern. The echoendoscopists were unaware of the results of histology and the pathologists were unaware of the results of EUS.

statistical analysis

Statistical differences were evaluated by Mann–Whitney test and chi-square test as appropriate. The post-treatment probability and the time required for complete response evaluated by EUS and E-Bx was calculated by the Kaplan–Meier method and comparison between the two groups was made with the log-rank test. A P value of <0.05 was considered significant.

results

Among patients affected by DLBCL, one (patient 1) did not respond to treatment and was lost to follow-up, one patient (patient 3) died of hepatic failure after 48 months while being in continuous complete remission (CCR) for lymphoma. The remaining five patients are alive in CCR as documented by E-Bx but every patient has persistence of EUS abnormality after a median follow-up of 44 months. Among patients affected by MALT, two had relapsed during follow-up (18 and 15 months, respectively, after having achieved CR) and have been treated with chemotherapy. One is again in CR (patient 11) and the other in PR (patient 10). In both cases, the relapse was contemporarily documented by EUS and E-Bx but none of these techniques was able to predict reappraisal of disease since both the EUS and the E-Bx were negative 9 and 3 months before relapse of each patient, respectively. One patient (patient 14) developed a mediastinal anaplastic lymphoma and obtained a second CR with a CHOP-like regimen. One patient (patient 17) had a relapse of MALT in small intestine (without gastric involvement) and reached a new CR with CHOP. One patient (patient 13) died of second neoplasm while being in CR for lymphoma. The remaining 11 patients are in continuous CR as documented by E-Bx after a median follow-up of 72 months but six of them have a positive EUS (Table 1). Therefore, in the entire series, among the 17 patients in CCR, 12 (six DLBCL and six MALT) have persistent abnormalities at EUS and the median follow-up of these patients is 36.5 months (Figure 1).

When the response was evaluated in the whole group, at the end of initial treatment a CR was documented in 15 (65%) patients by using E-Bx according to the definition indicated in the 'Materials and Methods' section. At the same time only two patients showed a normalization of EUS ($P = 0.0002$). Patients were then evaluated with EBs and EUS every 3/6 months and with a more prolonged follow-up (four patients) or the addition of further chemotherapy (two patients) a total of six patients in PR turned to CR so that the final number of patients in CR by E-Bx has increased to 21 (91%). At the same time, although EUS showed a reduction of median value of thickness of gastric wall from 1 to 0.6 cm ($P = 0.0031$), only seven patients (30%) had a normal EUS ($P < 0.0001$). In particular, during follow-up, EUS turned from positive to negative in five patients affected by MALT but in none of the DLBCL patients. Kaplan–Meier analysis showed that both the probability to obtain a CR and the time to achieve a CR were significantly different if the evaluation was done by E-Bx or by EUS (Figure 2). Median time

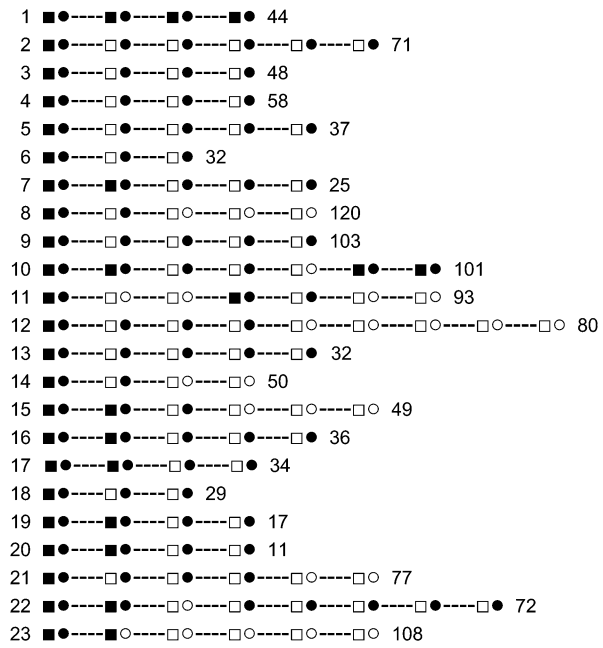

Figure 1. Schematic representation for each patient of results of concomitant evaluation by positive (■) or negative (□) endoscopy with biopsy and positive (●) or negative (○) endoscopic ultrasound. At the end of each line the duration of follow-up in months is indicated.

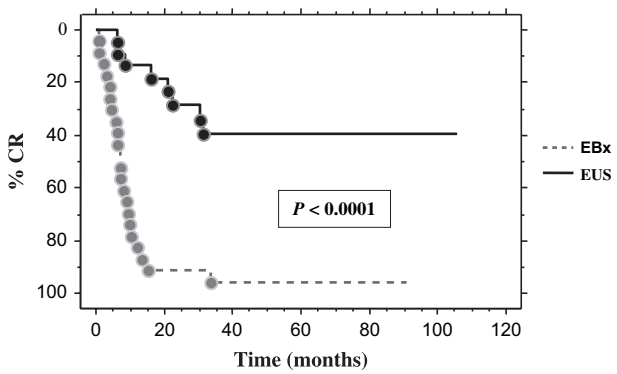

Figure 2. Time required for achieving a complete remission by endoscopy with biopsy (E-Bx) and endoscopic ultrasound (EUS) (Kaplan–Meier plot).

to obtain CR was 8 months when remission was assessed by E-Bx versus 20 months when assessed by EUS ($P = 0.005$).

We therefore compared the findings of EUS and E-Bx in order to verify the concordance of these two methods (Table 2). During follow-up of the 23 patients, a total of 99 contemporary evaluations of EUS and E-Bx have been carried out with a median number of 4 (range 2–7) for each patient and a median interval of 7 months (range 3–52 months). We separately analyzed the two histological groups of patients, namely DLBCL and MALT. A positive EUS has always been found during the follow-up in the seven DLBCL patients. In one of them there was evidence of disease at E-Bx and therefore there was concordance between the two methods but in the six remaining patients E-Bx has been maintained negative (and EUS positive) after a median follow-up time of 44 months (range 25–71).

Table 2. Concordance between EUS and E-Bx in defining complete response during follow-up

No. of patients	Type of disease	No. of examinations	Concordance			Discordance		
			EUS+ E-Bx+	EUS− E-Bx−	Total (%)	EUS+ E-Bx−	EUS− E-Bx+	Total (%)
7	DLBCL	24	4	0	4 (17)	20	0	20 (83)
16	MALT	75	9	20	29 (39)	44	2	46 (61)
23	Total	99	13	20	33 (33)	64	2	66 (67)

DLBCL, diffuse large-B-cell lymphoma; E-Bx, endoscopy with biopsy; EUS, endoscopic ultrasound.

In MALT patients the concordance between the two methods, both positive or both negative, was recorded in 29 occasions (39%) while a discordance was present in 46 evaluations (61%) and in 44 of them the EUS was positive while the E-Bx did not show any persistence of disease.

discussion

This report focuses on the reliability of EUS for evaluation of response to treatment and as a tool for follow-up evaluation in patients affected by localized gastric lymphoma and treated with a stomach-conserving approach. For the purpose of the study, we retrospectively evaluated both EUS and E-Bx findings in 23 patients and we found that in 67% of the total evaluations there was a discordance between the two methods that was almost exclusively represented by a positivity of EUS with a negativity of E-Bx. This discrepancy explains why at the final evaluation we found a complete remission of 91% of cases when patients were evaluated on the basis of the E-Bx versus a CR rate of 30% when judgment was based on the EUS findings. In addition, documentation of complete remission by EUS takes much longer than that by E-Bx (20 versus 8 months). These differences clearly imply that one of these methods is less reliable in documenting response to treatment and our results would indicate that E-Bx is more useful than EUS in this setting and a persistent abnormality of the EUS is not predictive of relapse. The duration of follow-up is in favor of this conclusion: among 12 patients with persistence of abnormal signal at EUS but a negative E-Bx, none has relapsed after a median follow-up of 36.5 months. We think that this follow-up is long enough to exclude early relapse. This is especially true for patients affected by DLBCL [19] that in our series has maintained a positive EUS throughout the time of our observation (44 months). In MALT lymphoma late relapses are possible but in a very small proportion [7] and it is likely that most of our patients affected by MALT lymphoma are cured from disease.

EUS is routinely carried out for staging evaluation of gastric lymphoma especially since a stomach-conservative approach has became the standard procedure and EUS is a useful tool for choosing the right treatment of each patient. On the contrary, few studies have evaluated the value and the reliability of this procedure in evaluating response to therapy and in the follow-up. In one study [9], post-treatment EUS documented an abnormal thickness of the wall in three out of 11 patients affected by MALT and two of the three patients had residual lymphoma. In another study [15], persistence of EUS changes in one case of MALT lymphoma was able to predict relapse of disease while E-Bx was negative. Therefore, authors concluded that the persistence of wall thickness at EUS is an indication for repeating biopsies in order to detect persistence of disease or early relapse. These and other small studies would indicate that EUS is a useful tool for follow-up evaluation and indicate that for patients in remission, with a restoration of normal gastric wall, a recurrent wall thickening at EUS might be indicative for relapse [14]. Our experience does not, however, confirm the above-mentioned studies since the relapse that occurred in two patients was not predicted by EUS nor by E-Bx. In addition, more recent studies, conducted in larger series, have reduced the importance of EUS in the setting of follow-up. A study [20] evaluated the application of a miniature ultrasound probe during the follow-up of 20 patients affected by MALT. Although the authors conclude that EUS is a valuable tool for the follow-up because it can document a decrease in wall thickness after eradication of HP, in this report half the patients showed persistence of significant abnormality at EUS even in the absence of endoscopic lesions. Another recent study [16] on a larger series indicated that the accuracy of EUS in evaluating remission of disease was inferior to histology, with a concordance between histology and EUS present in 64% of patients. In addition, the EUS findings returned to normal in a much more prolonged time in respect to gastroscopy with biopsy. After a prolonged follow-up, however, an EUS complete remission occurred in almost every patient. This latter finding is different from our experience where, even after a prolonged follow-up, although a significant reduction of thickness of the gastric wall was documented in most patients, the percentage of EUS complete remission remained very low in respect to E-BX remission. This difference might be explained in part by the fact that we considered any persistence of wall thickness as persistence of disease and it is possible that small thicknesses were evaluated in our series with too stringent criteria as evaluation of gastric EUS may be more subjective than EUS of other organs [21].

The persistence of EUS abnormality in histologically negative patients may be interpreted in two ways. The first is that EUS tends to overstage residual disease because it is not able to differentiate between tumor and fibrosis. Therefore, in our patients residual thickness of the gastric wall could represent a sort of scar of the previous disease and this hypothesis has to be considered especially for patients affected by DLBCL where a residual fibrotic tissue after therapy is a common finding in patients with nodal presentation of disease [22]. The second hypothesis is that EUS really detects a persistent lymphoma residue that is not evident at histological level because the lymphoma cells are limited in the submucosa or in the deeper

layers of gastric wall and it is not easy to catch them up with biopsy. This hypothesis is most likely for patients affected by MALT and is reminiscent of the persistence of lymphoid tissue monoclonality at the molecular level in MALT lymphomas that appear negative on histological grounds after eradication of HP. In several studies the persistence of a monoclonal pattern has been documented in roughly half the patients who have achieved a complete histological response after HP eradication but most of the studies indicate that this monoclonality tends to disappear in the majority of the patients during the follow-up [20, 23, 24], exactly as it happened in our EUS findings. The persistence of a monoclonal pattern detected by molecular tools despite a pathologic remission has also been recently reported in gastric MALT patients treated with radiotherapy. In this study [25] the authors make the hypothesis that therapy eliminates an important factor (maybe the T lymphocytes) essential for proliferation of the monoclonal B cells [26, 27]. Thus, it is possible that disappearance of lymphoma cells is a very slow process that takes several years to extinguish once the initiating factors have been eliminated. In any case, persistence of EUS abnormality after treatment, irrespective of the fact that it indicates fibrosis or minimal residual disease, does not have a clinical relevance since in our patients it has not been predictive of relapse and should not be used as a guidance for further treatment.

In conclusion, we think that EUS is very helpful for staging of disease but its role in evaluating response to treatment is questionable. In restaging and follow-up, EUS seems not to be a reliable tool if it is abnormal and E-Bx still remains the gold standard. After conventional conservative treatment, persistence of EUS abnormality with a negative histology should not be considered as a clinically relevant persistence of disease and should not be a reason for further treatment. Our study is, however, retrospective and also lies in a small number of cases. A prospective study should be carried out with an adequate number of patients so as to distinguish between DLBCL and MALT since the two diseases have different therapeutic approaches. For the time being, we think that patients with gastric lymphoma treated with a conservative approach should still be followed with both EUS and E-Bx in order to have a longer follow-up and more information on the role of EUS in detecting early relapse.

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