

Role of ^{18}F -FDG PET Scans in Patients with *Helicobacter pylori*-Infected Gastric Low-Grade MALT Lymphoma

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Background/Aims: Endoscopic ultrasound (EUS) plays a crucial role in the assessment and treatment of low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma; however, interobserver variation, inadequate accuracy in judging the depth of tumor invasion, and histological heterogeneity of the tumor can limit its role. Thus, we have assessed the role of ^{18}F -FDG PET scans in the management of *Helicobacter pylori*-infected gastric MALT lymphoma. **Methods:** Eighteen patients with *H. pylori*-infected low-grade gastric MALT lymphoma underwent an ^{18}F -FDG PET scan prior to receiving *H. pylori* eradication therapy. We analyzed these patients' clinicopathologic data and measured the baseline and change in the metabolic activity of the tumor using standardized uptake values (SUVs). **Results:** Two patients failed to achieve complete remission of the low-grade gastric MALT lymphoma after successful *H. pylori* eradication. The baseline SUVs were significantly higher in these patients compared to successfully treated patients, 13.35 ± 0.07 vs 2.98 ± 0.93 , respectively ($n=2$ vs $n=16$, $p<0.001$). The reduction in the SUV was significantly greater in the complete remission patients compared to treatment failure patients ($p=0.018$). **Conclusions:** A high SUV at baseline ^{18}F -FDG PET and a lower reduction in the SUV within 3 months after eradication therapy are associated with treatment failure in *H. pylori*-positive low-grade gastric MALT lymphoma patients undergoing eradication treatment. (*Gut Liver* 2011;5:308-314)

Key Words: MALT lymphoma; *Helicobacter pylori*; Treatment failure; Positron emission tomography

INTRODUCTION

The low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent tumor, which is strongly associated with *Helicobacter pylori* infection.¹ *H. pylori* eradication is a well-established initial treatment modality in *H. pylori*-positive low-grade gastric MALT lymphoma confined to the gastric mucosa or submucosa. Many reports affirm that eradication treatment alone shows a greater than 80% complete remission (CR) rate and durable remission. Although the majority of the tumors regress within 1 month of eradication therapy, the achievement of CR may take up to one year. Some experts define residual MALT lymphoma lasting over one year after *H. pylori* eradication as treatment failure.² Since there are patients with tumors demonstrating a mixture of low-grade MALT lymphoma and diffuse large B cell lymphoma (DLBCL) on histopathological examination, such a long period of waiting for CR after *H. pylori* eradication therapy poses the risk of tumor progression. It is important, therefore, to define the clinicopathologic factors related with initial treatment failure by *H. pylori* eradication. To date, the factors known to be related to initial treatment failure in low-grade gastric MALT lymphoma are as follows: MALT lymphoma not related with *H. pylori* infection, deeper tissue invasion, and genetic abnormalities such as $t(11;18)$.³⁻⁵

Determining the depth of tumor invasion, while important in predicting the response to *H. pylori* eradication treatment, poses some diagnostic challenges. Scanning the entire stomach is often technically difficult, and deeper invasive lesions of synchronous, multicentric gastric MALT lymphomas may be missed during scanning with endoscopic ultrasound (EUS). Also, recent data show suboptimal interobserver agreement in assessing the

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depth of tumor invasion of gastric MALT lymphomas by EUS.⁶ Furthermore, the histological heterogeneity of the tumor makes it difficult to choose an appropriate treatment modality. Proportions of large cell histology within the MALT lymphoma tissue determine the prognosis⁷ and the classification of MALT lymphoma.⁸ The failure to recognize large cell aggregates on biopsy often misleads physicians, causing them to initiate ineffective therapies against 'hidden' much more aggressive neoplasm.^{9,10}

¹⁸F-FDG PET scan is widely used as a cancer staging modality. By assessing the metabolic status of the stomach collectively, PET scan may provide additional information of proportion of large cell aggregates which has relatively higher metabolic activity and may not be regressed by *H. pylori* eradication. PET scans also can be useful in predicting the response to cancer treatment early in the course of therapy.¹¹ Here, we assess the role of PET scan in planning treatment modalities of *H. pylori*-associated low-grade gastric MALT lymphoma.

MATERIALS AND METHODS

From May 1992 to September 2005, 71 patients were diagnosed with primary gastric low-grade MALT lymphoma by histopathological exam at Yonsei University, Severance Hospital. Among them, 26 patients underwent an ¹⁸F-FDG PET scan before any anti-tumor treatments. Eight patients underwent initial

treatment other than *H. pylori* eradication and were excluded from analysis. We analyzed the clinical data in the remaining 18 patients with *H. pylori*-positive low-grade gastric MALT lymphoma. Patients diagnosed with mixed pathology with diffuse large B cell lymphoma or who were found to have secondary involvement of the stomach from systemic disease were excluded from the analysis.

All the patients' ¹⁸F-FDG PET scans were performed with a GE[®] advanced PET scanner, after 60 minutes from injection of 0.068-0.14 mCi/kg of ¹⁸F-FDG. Some patients received another follow-up PET scan within 3 months from the end of initial treatment. The quantification of FDG uptake (standardized uptake value, SUV) was conducted by one nuclear medicine expert. Most of the patients (15 out of 18) underwent EUS as part of an initial staging exam. EUS was performed with radial sector scanning echoendoscopes (GFUM-240, GFUM-2000; Olympus, Tokyo, Japan) with variable frequencies of 5, 7.5, 12, and 20 MHz or Miniprobe[®] with a frequency of 20 MHz. Acoustic coupling with the gastric wall was obtained by using a water-filling technique or using a water-filled balloon on the instrument's tip. A bone marrow exam was also included in the staging evaluation. *H. pylori* infection was considered to be present if either histology, rapid urease test, or a ¹³C-urea breath test was positive.

All of the patients underwent *H. pylori* eradication therapy

Table 1. Clinical Characteristics and Treatment Results

Patient no.	Sex	Age	EUS*		Pattern of lesion	FDG uptake (SUV)			Initial Tx result [†]
			T	LN		Baseline	Follow-up	Change	
1	F	34	M	-	Erythematous, localized	2.7	2.8	0.1 (3.7%)	CR
2	F	58	M	+	Ulcerative, multicentric	1.8	ND	ND	CR
3	F	70	ND	ND	Erosive, localized	3.0	ND	ND	CR
4	M	74	ND	ND	Erythematous, multicentric	3.0	ND	ND	CR
5	M	48	SM	-	Ulcerative, localized	4.0	3.0	-1.0 (-25.0%)	CR
6	M	48	M	-	Polypoid, localized	1.8	1.6	-0.2 (-11.1%)	CR
7	F	46	SM	-	Ulcerative, localized	2.4	1.4	-1.0 (-41.7%)	CR
8	M	40	SM	-	Ulcerative, multicentric	2.0	1.2	-0.8 (-40.0%)	CR
9	F	52	SM	+	Protruding, multicentric	13.3	15.3	2.0 (15.0%)	Failure
10	F	39	M	-	Erythematous, diffuse	2.5	3.0	0.5 (20.0%)	CR
11	F	47	M	-	Erythematous, localized	3.5	1.2	-2.3 (-65.7%)	CR
12	M	52	SM	-	Erosive, localized	4.8	4.3	-0.5 (-10.4%)	CR
13	F	62	M	-	Erythematous, diffuse	3.2	2.7	-0.5 (-15.6%)	CR
14	F	46	M	-	Ulcerative, diffuse	4.2	ND	ND	CR
15	M	54	SM	-	Ulcerative, diffuse	2.5	ND	ND	CR
16	F	67	ND	ND	Protruding, localized	4.2	ND	ND	CR
17	F	64	SM	-	Ulcerative, diffuse	2.1	2.6	0.5 (23.8%)	CR
18	F	72	B	-	Ulcerative, diffuse	13.4	ND	ND	Failure

*Endoscopic ultrasound findings (M, mucosal; SM, submucosal; B, beyond SM; ND, no available data); [†] Result of initial treatment (CR, complete remission).

as anti-tumor treatment. Therapy consisted of a seven or 14-day course of triple therapy with rabeprazole (20 mg b.i.d.), amoxicillin (1,000 mg b.i.d.), and clarithromycin (500 mg b.i.d.). After the completion of eradication treatment, follow-up endoscopic examinations were performed at 3-6 month intervals or annually if sustained remission was achieved. Initial treatment failure was defined as the presence of aggressive histopathology other than low-grade MALT lymphoma on follow-up biopsy or persistence of low-grade MALT lymphoma in biopsy specimens at one year post-treatment. Data were expressed as a mean \pm SD. Statistically significant differences were determined by Student's t-test or two-tailed Fisher's exact test. Statistical analysis was performed with SPSS Statistical Package, version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 18 patients were diagnosed with primary low-grade gastric MALT lymphoma on multiple endoscopic biopsies. All the cases were *H. pylori*-infected. The depth of tumor invasion and presence of other organ involvement were assessed before the initiation of *H. pylori* eradication therapy (Table 1). One patient (patient number 4) had concomitant MALT lymphoma of the bronchus, and the remaining patients had no synchronous lesion in other organs.

After the completion of initial eradication treatment, 16 patients achieved CR with no need for additional treatments. The two patients were defined as treatment failures. Despite completing *H. pylori* eradication treatment, one patient had biopsy results consistent with residual low-grade MALT lymphoma at 10-month follow-up, and radiation therapy was then initiated. The follow-up biopsy of another patient with treatment failure showed progression into the DLBCL, and the patient was assigned to receive intravenous chemotherapy (Fig. 1).

The treatment failure group tended to be older than the CR group, but this was not statistically significant ($p=0.331$, Table 2). Depth of tumor invasion, as determined by EUS, was divided into two stages, tumors limited to the mucosa and tumors extending beyond the mucosa. We failed to find any significant difference in the depth of tumor invasion between the two groups. On the other hand, baseline FDG uptake was significantly higher in the treatment failure group compared to CR group, 13.35 ± 0.07 SUV vs 2.98 ± 0.93 SUV, suggesting significantly higher metabolic activity in the treatment failure group ($p<0.001$). A more evident reduction of FDG uptake was achieved in the CR group (-0.52 ± 0.84 SUV, $-16.2\%\pm 28.1\%$) compared to the treatment failure group, and one treatment failure patient showed 15.0% increase in FDG uptake in a post-treatment PET scan ($p=0.018$, Table 2, Fig. 1). Patients who demonstrated tumor regression after *H. pylori* eradication therapy had less baseline FDG uptake and a more marked decrease in uptake after therapy than the treatment failure group (Table

2, Fig. 2). After the achievement of complete remission, no recurrence was seen in any of the 18 patients during the median

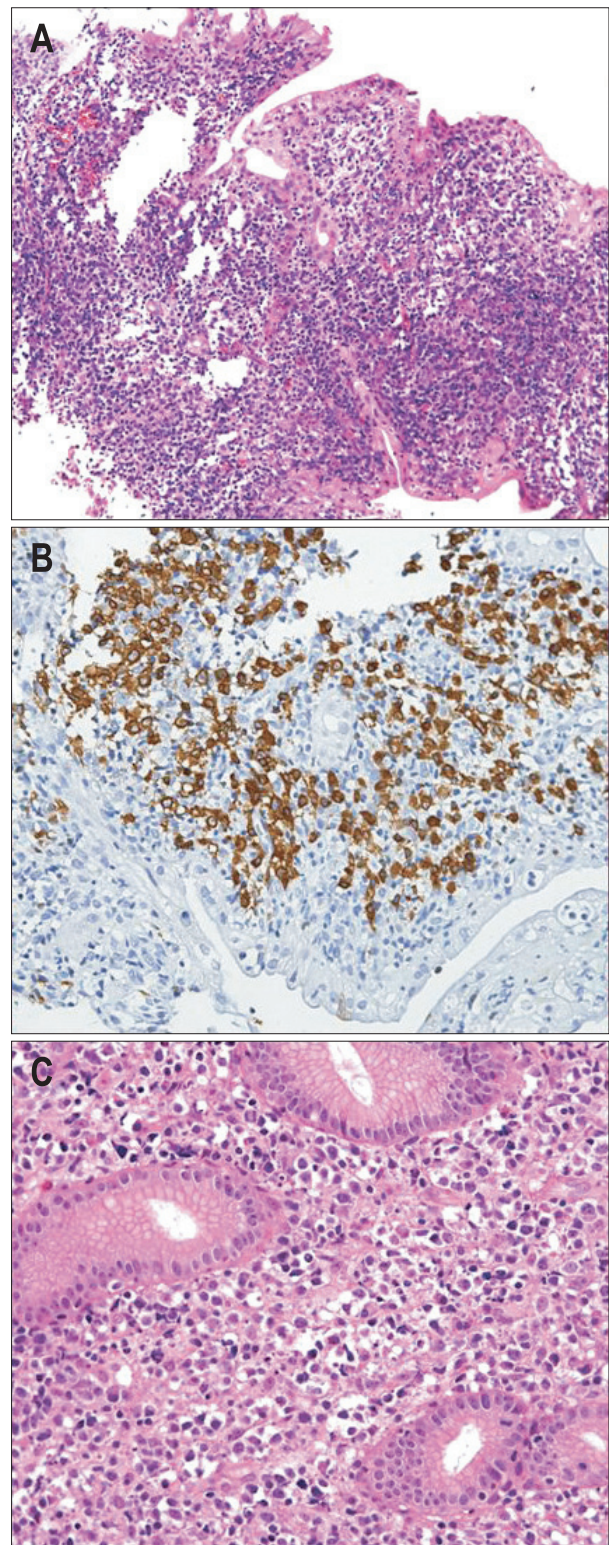


Fig. 1. The initial biopsy is consistent with low-grade mucosa-associated lymphoid tissue (MALT) lymphoma by H&E staining ($\times 100$) (A) and by immunohistochemical staining for L26/CD79a-positive, CD3-negative cells ($\times 200$) (B), but a subsequent study confirms the diagnosis of diffuse large B cell lymphoma ($\times 200$) (C).

Table 2. Comparison of the Complete Remission Group with the Treatment Failure Group

Eradication group	CR group (n=16)	Treatment failure group (n=2)	
Age	53.1±11.7	62.0±14.1	p=0.331
<i>H. pylori</i> positivity	16/16 (100%) M=7/13*	2/2 (100%) M=0/2	NA
Depth of invasion by EUS	beyond M=6/13* (SM=6/13, beyond SM=0/13)	beyond M=2/2 (SM=1/2, beyond SM=1/2)	p=0.467
Baseline SUV	2.98±0.93	13.35±0.07	p<0.001
Change of SUV	-0.52±0.84 [†] (-16.2±28.1%) [†]	2.0 [‡] (15%) [‡]	p=0.018 (p=0.317)

EUS, endoscopic ultrasound; SUV, standardized uptake value.

*Only 13 patients out of 16 were studied by EUS; [†]Only 10 patients out of 16 were studied by follow-up PET; [‡]Only one patient out of 2 was studied by follow-up PET.

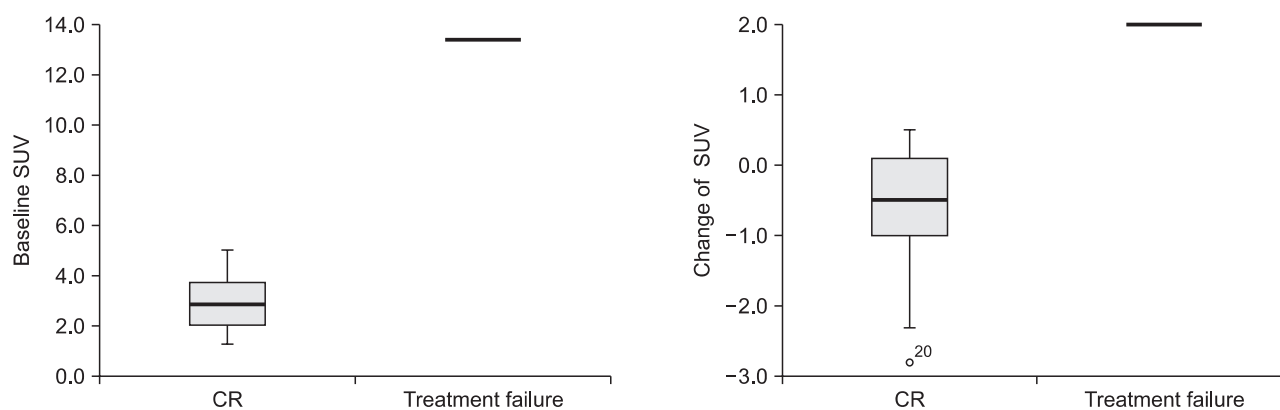


Fig. 2. Baseline standardized uptake values (SUVs) and changes in the SUV according to clinical outcome. The boxes represent the 25th and 75th percentile, the thick horizontal bars represent the median, and the upper and lower horizontal bars represent the maximum and minimum data. CR, complete remission.

follow-up of 25.4 months (range, 1.3 to 82.8 months).

DISCUSSION

Primary gastric lymphoma represents the most common presentation of extranodal lymphoma. *H. pylori* infection is strongly associated with low-grade gastric MALT lymphoma, and regression of the tumor has been reported in 50% to 100% of patients after eradication therapy. There is a higher risk of treatment failure, if MALT lymphoma is not related with *H. pylori*, has deeper tissue invasion, or is associated with a genetic abnormality such as t(11;18).³⁻⁵ There are some low-grade MALT lymphomas that exist in combination with diffuse large B cell lymphoma, which can progress during the follow-up period after eradication therapy. It has clinical impact, therefore, to define clinicopathologic parameters in low-grade gastric MALT lymphoma that correlate with those tumors that do not respond to *H. pylori* eradication therapy.

Application of a PET scan with the glucose analog ¹⁸F-FDG for cancer staging or assessment of therapy response is widely accepted in the majority of cases of solid cancers and lympho-

mas.^{12,13} By estimating the baseline or changes in SUV, PET scan allows clinicians to predict or monitor treatment response early in the course of therapy. Some studies have already reported the useful role of ¹⁸F-FDG PET scan in MALT lymphoma.¹⁴⁻¹⁶ But these studies consisted of primary tumors arising from heterogeneous organs and included only nine to ten primary gastric MALT lymphoma patients. This is the largest case series ever, including only primary gastric MALT lymphoma. More importantly, this is the first report that shows that metabolic imaging correlates with clinical outcomes in patients with low-grade gastric MALT lymphoma. Our results demonstrated that a baseline PET scan, with or without follow-up imaging after treatment, allows for the prediction of tumor response to *H. pylori* eradication therapy in patients with gastric low-grade MALT lymphoma. High SUV on baseline PET scan or lower degrees of reduction in SUV within 3 months after the eradication treatment were associated with treatment failure.

EUS plays an important role in the staging of MALT lymphoma, and it is the best diagnostic modality to guide the initial treatment course and to help determine the need to change the treatment plan. Despite this fact, a multicenter evaluation of in-

terobserver agreement with respect to endosonographic staging of gastric MALT lymphoma revealed suboptimal results.⁶ The kappa value of submucosal or deeper lesions were below 0.40, even down to 0.20 after treatment, and that of mucosal lesions was around 0.40. Whether the depth of tumor invasion should be a risk factor for disease progression still remains controversial. Recently, El-Zahabi *et al.*¹⁷ analyzed 19 *H. pylori*-positive patients with gastric MALT lymphoma and demonstrated that tumors with submucosal infiltration have a significantly lower rate of complete remission after eradication compared with mucosal lesion (12.5% vs 77.8%, $p=0.007$). Another study showed that most gastric lymphomas restricted to the submucosa achieved complete remission, whereas deeper tissue invasion beyond the submucosal layer failed to show remission.¹⁸ On the other hand, another report demonstrated that the absence of nodal involvement is the only predictor of tumor regression with multivariate analysis.⁴ Given the suboptimal interobserver agreement and the need for a highly skilled endosonographer and the undetermined value of the depth of tissue invasion in determining the risk of tumor progression, the role of EUS in judging the treatment response in low-grade gastric MALT lymphomas remains unclear.

Histological heterogeneity is another obstacle in planning the treatment of gastric MALT lymphomas. The amount and pattern of large-cell populations within MALT lymphoma tissue differentiates low-grade MALT lymphoma from the much more aggressive DLBCL. MALT lymphoma containing over 5-10% large cells is known to indicate a worse prognosis.^{7,8} The distribution of large cells within the neoplasm is extremely heterogeneous,⁹

and it is well known that MALT lymphoma involvement in the stomach is sometimes multifocal or diffuse.¹⁹ Therefore, it is no surprise that there is a significant discrepancy in the diagnosis between surgical and endoscopic samples, and the difference seems not to be overcome by multiple biopsy samples.^{7,10}

Overcoming the limits of EUS and the histological heterogeneity of the tumor is critical, and we demonstrate that the ¹⁸F-FDG PET scan can be a tool to assess the stomach as a whole. In this study, the baseline SUV of patients in the CR group was very low, 2.98 ± 0.93 (range, 1.8 to 4.8). This relatively low metabolic activity may indicate that tumors in this group have a low large-cell component, which correlates with a good response to *H. pylori* eradication therapy in these patients.

We observed two patients who failed to achieve remission during follow-up. Their baseline SUVs were higher than 13.0, and this indicated that their lesions expressed significantly higher metabolic activity. Again, this possibly indicates that the tumors may contain a relatively greater large-cell component, which may not be detected by sampled biopsies. Failure to recognize these more aggressive histopathological features may lead to ineffective treatment courses and a greater risk of disease progression. One of the patients within this study who failed to respond to *H. pylori* eradication therapy showed progression to a DLBCL (Fig. 3), and achieved remission after a series of combination intravenous chemotherapy. It is likely that the patient's initial biopsy samples did not include the heterogeneously distributed large-cell portion, leading to the misdiagnosis of a DLBCL as a low-grade MALT lymphoma. This underscores the obvious need to overcome the histological heterogeneity of these

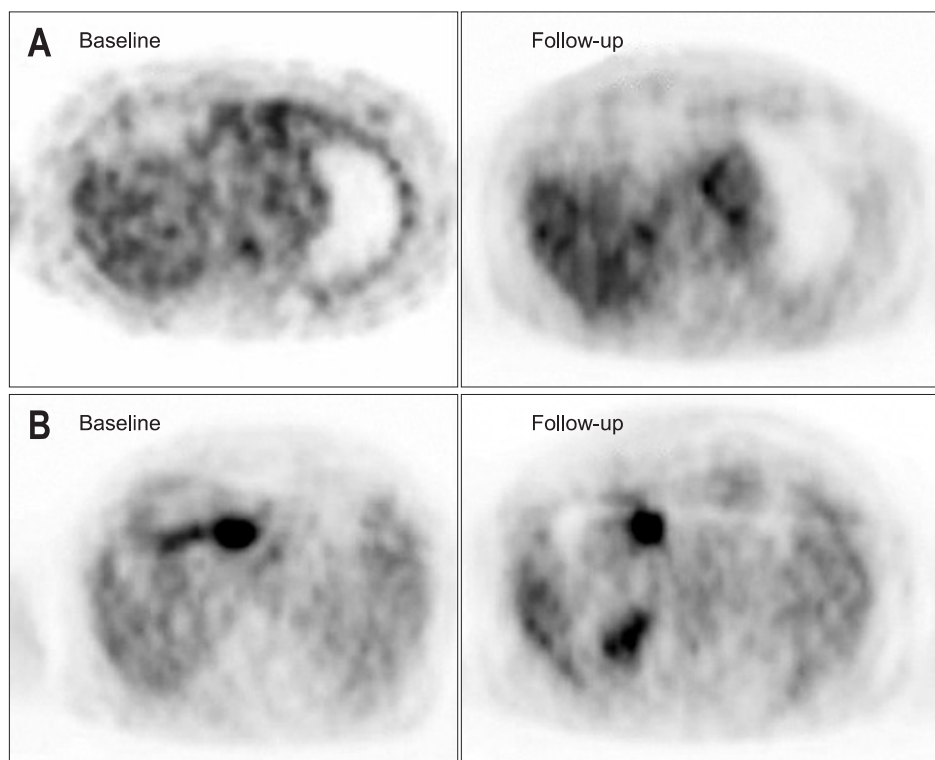


Fig. 3. Examples of baseline and follow-up PET images. (A) Patient number 7. The stomach wall shows diffusely increased uptake from baseline (baseline standardized uptake value [SUV], 2.4) that become fainter after eradication therapy (follow-up SUV, 1.4). Complete remission is maintained during the 30-month follow-up. (B) Patient number 9. High-grade FDG uptake is noted at the antrum (baseline SUV, 13.3). Even after eradication therapy, a residual low-grade mucosa-associated lymphoid tissue (MALT) lymphoma persists. The high baseline SUV correlates with follow-up images (follow-up SUV, 15.3). This patient fails to gain complete remission during the 10-month follow-up period after the initiation of treatment.

tumors through alternative diagnostic modalities. PET scanning assesses the metabolic status of the stomach collectively. These images may indicate the status of sporadically distributed large cells within the stomach and minimize the misdiagnosis of DLBCL as low-grade MALT lymphoma. Although not included in our study, we encountered another case of gastric DLBCL in a 63-year-old female patient. Her initial biopsy was consistent with low-grade MALT lymphoma. Baseline FDG uptake in that patient was relatively high, 11.1 SUV, and immediate repeat endoscopic reexamination confirmed that the tumor was actually DLBCL. By identifying high baseline metabolic activity and initiating radiation therapy or chemotherapy, the risk of delaying treatment while waiting for as long as 12 months after the eradication therapy² to achieve MALT remission can be avoided.

By quantification of FDG uptake, expressed as SUV, it is possible to compare the degree of uptake and to measure the change in value in the same subject. Some studies have shown that chemotherapy-resistant tumors show a relatively higher pretreatment SUV or less degree of reduction in SUV after treatment. These findings suggest the need to alter treatment modalities early in the clinical course.¹¹ Unfortunately, at present, there are no generally accepted criteria for a metabolic response in FDG-PET studies, and it should be established for every specific neoplasm. In a study evaluating 50 lesions,²⁰ a change in SUV can be considered significant only when the difference between the baseline and follow-up PET scan is more than 0.9. For the eleven patients with low-grade MALT lymphoma who underwent follow-up PET, only a small reduction in SUV (-0.18 ± 1.10 SUV; range, -2.3 to 2.0 SUV) was noted in this study. These data demonstrated that the utility of PET scans in the early identification of tumors with poor response to eradication therapy may be suboptimal for indolent low-grade gastric MALT lymphomas. It may be more reasonable to use baseline ¹⁸F-FDG PET results as a tool to predict treatment failure with *H. pylori* eradication therapy and to determine whether this treatment course should be pursued in patients with gastric low-grade MALT lymphoma. Furthermore, PET might discriminate MALT lymphoma with a substantial large-cell component responding to eradication treatment from a non-responding tumor. Some reports and a prospective study showed early stage DLBCL with features of MALT lymphoma that would regress after *H. pylori* eradication therapy,²¹⁻²³ but this remains uncertain. In that context, using PET imaging may be of some utility in detecting tumors with low metabolic activity reflecting, DLBCL mixed with a low-grade MALT lymphoma component, which might respond to *H. pylori* eradication therapy. We have encountered two patients with gastric DLBCL with SUV below 5.0 (data not included; 4.1 and 4.9 SUV, mucosal and submucosal invasion on EUS, respectively) who regressed into low-grade MALT lymphoma on gastrectomized pathology or follow-up endoscopic biopsies.

In conclusion, we have examined the role of ¹⁸F-FDG PET scan in formulating treatment options for low-grade gastric

MALT lymphomas with *H. pylori* infection. Patients with high baseline SUV or less of a decline in SUV after *H. pylori* eradication treatment showed a significantly higher rate of treatment failure. By defining high metabolic activity, a baseline PET scan may suggest a MALT tumor with histologic features consistent with DLBCL as well. Baseline PET scans may be of great utility in treatment planning for patients with low-grade gastric MALT lymphoma, especially when mixed cellularity with DLBCL is suspected. We suggest that physician do re-biopsy or re-staging if the initial lesion has intense FDG uptake on PET scan.

Our study has some limitations. This study was limited by a small number of subjects, and with only two treatment failure cases, it is impossible to compare the range of baseline SUV and changes in SUV. In addition, only 11 patients were followed with PET imaging. Consequently, no cutoff value for discriminating responders from non-responders could be obtained. Also cost-effectiveness of performing PET in patient with low grade MALT lymphoma is a matter to be concerned. The Korean National Insurance Corporation has covered most of the fee of PET scan and only about twenty US dollars are charged to patients. But this is not the case in many other countries. We suggest physician perform PET scan especially in patients having diffuse lesion that may be hard to scan all properly with EUS, suspicious deep invasion, or mixed cellularity with DLBCL. Even with these shortcomings, this is the largest case series ever consisting with only gastric low grade MALT lymphoma, and it is remarkable that this is the first report suggesting metabolic image correlate with clinical outcomes of eradication therapy. It is warranted to conduct a well-designed, prospective study with a statistically sufficient sample size to determine that PET image can overcome the clinical limit of EUS in managing gastric MALT lymphoma.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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