

Clinical impact of genetic aberrations in gastric MALT lymphoma: a comprehensive analysis using interphase fluorescence *in situ* hybridisation

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Background and aims: There is a need for genetic biomarkers to guide prognosis and management of gastric mucosa-associated lymphoid tissue (MALT) lymphomas. We assessed the incidence and clinical significance of the MALT lymphoma-associated genetic abnormalities t(11;18)/API2-MALT1, t(1;14)/BCL10-IGH, t(14;18)/IGH-MALT1, t(3;14)/FOXP1-IGH, and extra copies of MALT1 and FOXP1 in gastric MALT lymphomas from Japan.

Methods: The presence of translocations and copy number changes involving MALT1, IGH and FOXP1 were assessed in 90 cases of gastric MALT lymphoma using interphase fluorescence *in situ* hybridisation (FISH). In cases carrying a MALT1 translocation, FISH for API2-MALT1 was performed, whereas in those carrying an IGH translocation, FISH was performed for BCL10, BCL6, BCL2, c-MYC and/or CCND1.

Results: t(11;18)/API2-MALT1 was detected in 18 of 87 (21%) cases and was significantly associated with *Helicobacter pylori*-negativity, resistance to *H pylori* eradication and Bcl10 nuclear expression. Four of 68 (6%) cases carried a translocation involving IGH and FOXP1 (n=1), BCL2 (n=1) or an unknown partner (n=2). Neither t(1;14)/BCL10-IGH nor t(14;18)/IGH-MALT1 was detected. Extra copies of MALT1 and FOXP1 were detected in 18 of 71 (25%) cases and 10 of 59 (17%) cases, respectively. The presence of extra copies of MALT1 was significantly associated with progression or relapse of lymphoma, and was an independent adverse prognostic factor for event-free survival as determined by multivariate analysis.

Conclusions: t(11;18)/API2-MALT1 is frequent, whereas IGH-involved translocations are rare in gastric MALT lymphoma in Japan. The presence of extra copies of MALT1, often suggestive of partial or complete trisomy 18, is a frequent genetic aberration in gastric MALT lymphoma, which appears to predict adverse clinical behaviour.

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) of the stomach is the most common low grade lymphoma.^{1,2} Although most patients with gastric MALT lymphoma experience an indolent clinical course, there is considerable individual variability in the extent of disease, response to treatment, relapse and event-free survival such that, for many, the optimal management is unclear. There is therefore a need for improved understanding of the genetic abnormalities underlying gastric MALT lymphoma and for new genetic biomarkers able to guide prognosis and management.

MALT lymphoma is genetically characterised by four chromosome translocations.^{1,2} The t(11;18)(q21;q21) generates a functional API2-MALT1 fusion transcript, whereas the other three translocations involve translocation to immunoglobulin gene loci and consequently increased expression of BCL10 (1p22), MALT1 (18q21) and forkhead box protein P1 gene (FOXP1) (3p14). Bcl10 and MALT1 proteins are involved in surface immune receptor-mediated activation of the nuclear factor kappa B (NF-κB) transcription factor; the chromosomal translocations involving these genes are believed to exert their oncogenic activities through constitutive activation of the NF-κB pathway, leading to expression of a number of genes important for cell survival and proliferation. FOXP1 is an essential regulator of early B cell development but the molecular mechanism underlying its oncogenic activities remains unknown.³ The above translocations occur at variable

frequencies in MALT lymphoma of different sites.^{4–8} Nonetheless, the majority of MALT lymphomas are negative for these translocations. Instead, these cases often harbour partial or complete trisomies of chromosome 3, 12 and 18.^{4,9,10}

The incidence of chromosome translocations in gastric MALT lymphoma has been described mainly from Western countries.^{4,5,7,8} In gastric MALT lymphoma, t(11;18)/API2-MALT1 has been detected frequently in Europe (15–24%),^{4,5,11} but is relatively rare in the USA (5%).⁸ However, the incidence of other MALT lymphoma-associated translocations and numerical abnormalities in gastric MALT lymphoma is less well established, particularly in Asian populations. The clinical impact of t(11;18)/API2-MALT1 is well characterised: gastric MALT lymphomas with this translocation are usually unresponsive to *H pylori* eradication, often present with advanced disease and rarely undergo high-grade transformation.^{12,13} In contrast, there is little information on the clinical features of gastric MALT lymphomas bearing other translocations or numerical changes affecting chromosomes 3 and 18.

In order to address these issues, we have investigated a large, homogenous, well-characterised cohort of 90 Japanese cases of gastric MALT lymphoma for all reported MALT

Abbreviations: CR, complete remission; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FISH, fluorescence *in situ* hybridisation; FOXP1, forkhead box protein P1; MALT, mucosa-associated lymphoid tissue; NF-κB, nuclear factor kappa B; OS, overall survival; RT-PCR, reverse-transcription polymerase chain reaction

lymphoma-associated translocations and numerical changes at *MALT1* and *FOXPI* loci, using interphase fluorescence *in situ* hybridisation (FISH), and examined the clinical impact of such genetic aberrations in detail.

METHODS

Subjects

Between 1966 and 2005, 380 consecutive Japanese patients with primary gastric lymphoma were diagnosed at Kyushu University. Among them, 206 cases of MALT lymphoma and/or diffuse large B-cell lymphoma (DLBCL) had formalin-fixed paraffin-embedded tissues and their histological diagnosis was reviewed according to the diagnostic criteria outlined in the World Health Organization classification.¹⁴ As a result, 90 cases of MALT lymphoma without any evidence of a DLBCL component were identified and enrolled in the present study. Some of these patients were included in previous studies.^{15–19}

Patients consisted of 47 men and 43 women, ranging in age from 16 to 80 years (mean 58 years). Depth of tumour invasion was determined by histological examination of the resected specimens or by endoscopic ultrasonography;¹⁶ 37 lymphomas were considered to be restricted to the mucosa and the superficial portion of the submucosa,^{15 16} 27 invaded the deep layer of the submucosa, 14 involved the muscularis propria and 12 reached the subserosa or serosa. A physical examination to determine the staging included an inspection of Waldeyer's ring, chest radiographs, abdominal ultrasound, computed tomography of the chest and abdomen, colonoscopy, small bowel barium radiography, bone marrow aspiration or biopsy, and gallium scintigraphy or fluorine-18 fluorodeoxyglucose positron emission tomography. According to the Lugano International Conference classification for clinical staging of gastrointestinal lymphoma,²⁰ 61 cases were classified as stage I, 19 as stage II₁, 6 as stage II₂, none as stage IIE and 4 as stage IV (involving bone marrow in 2, cervical lymph nodes in 1 and lung in 1). *H pylori* infection was judged as positive if one of any pretreatment tests for *H pylori*, including both serology and histology, showed a positive result, and as negative only when all tests were negative. A total of 69 of 78 patients (88%) were positive and 9 patients (12%) were negative for *H pylori*. The remaining 12 patients were not evaluated for *H pylori*.

Thirty-five (39%) patients underwent antibiotic treatment for eradication of *H pylori* with a proton pump inhibitor (omeprazole, lansoprazole or rabeprazole) plus a combination of antibiotics (clarithromycin and amoxicillin with or without metronidazole). Follow up endoscopic examinations with biopsies after eradication were performed every 4 to 8 weeks until confirmation of complete remission (CR), and they were repeated every 3 to 6 months after CR. CR was defined as a complete disappearance of clinical evidence of lymphoma and an absence of histological evidence of lymphoma on biopsy specimens. Partial remission was defined as a tumour reduction of at least 50%. Twenty-one of the 35 patients underwent eradication therapy alone, whereas 14 non-responsive patients then received radiotherapy (n = 6), oral monochemotherapy with cyclophosphamide (n = 6),¹⁷ multi-agent chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone plus rituximab (n = 1) or gastrectomy (n = 1). The remaining 55 patients (61%) were initially treated by gastrectomy with (n = 15) or without (n = 40) chemotherapy.

This study was carried out in accordance with the Helsinki Declaration as revised in 1989 and with the ethical guidelines of the participating centres and countries. Informed consent was obtained from each patient on the aims and the protocol of the study.

Interphase FISH

MALT lymphoma-associated chromosome translocations were investigated by interphase FISH on formalin-fixed paraffin-embedded tissues as described previously.^{10 21} In each case, the hybridisation signals for each probe were evaluated in at least 100 nuclei. Initially, translocations were screened by FISH with dual-colour break-apart probes for *MALT1*, *IGH* (Vysis/Abbott Laboratories Ltd, UK) and *FOXPI*. The genomic bacterial artificial chromosome clones used as the *FOXPI* probe were described previously.²² In cases positive for a *MALT1* gene break, additional FISH with dual-colour, dual-fusion translocation probe for *API2/MALT1* (Vysis/Abbott) was performed, whereas in those positive for an *IGH* gene break, further FISH was carried out with dual-colour break-apart probes for *BCL6*, *BCL2*, *cyclin (CCN) D1*, *c-MYC*, (Vysis/Abbott) and *BCL10* (provided by Reiner Siebert, Kiel, Germany). A *FOXPI/IGH* dual-colour, dual-fusion translocation probe was developed in-house. For FISH with *MALT1* and *FOXPI* break-apart probes, numerical gains at chromosomes 18q21 and 3p14 were also evaluated. The threshold for positivity using each probe was the mean percentage of cells with false positive signals plus 3 standard deviations, as assessed on sections from 8 to 10 reactive tonsils.¹⁰

Reverse-transcription polymerase chain reaction

Reverse-transcription polymerase chain reaction (RT-PCR) for t(11;18)(q21;q21) was carried out to assess samples showing no signals by FISH with *MALT1* probe and to confirm FISH detected *API2-MALT1* translocations. Total RNA extraction from formalin-fixed paraffin-embedded tissues, complementary DNA synthesis and PCR for the *API2-MALT1* fusion transcript were performed as described previously.¹² RNA quality was assessed by RT-PCR of the control gene glucose-6-phosphate dehydrogenase. PCR products were analysed by electrophoresis on 10% polyacrylamide gels. We have previously shown that RT-PCR and FISH have similar sensitivity and specificity for the detection of t(11;18)/*API2-MALT1*.⁵

Immunohistochemistry

Immunohistochemical staining for Bcl10 was performed by the streptavidin–biotin complex method using a mouse monoclonal antibody (clone 151) on formalin-fixed paraffin-embedded tissues in all 90 cases as described previously.²³

Prognosis and statistical analysis

Overall survival (OS) was measured from the date of diagnosis to death from any cause. Event-free survival (EFS) was measured from the date of diagnosis to disease progression, relapse or death from any cause. Probabilities of OS and EFS for patients were calculated by the Kaplan-Meier method and the value was compared using the log-rank test. All variables with p < 0.1 were put into a multivariate analysis using the Cox proportional hazards regression model. Model selection for identifying the subset of significant variables was based on a forward stepwise procedure using the maximum likelihood ratio test. Other statistical differences were evaluated by Fisher's exact probability test, the χ^2 test or the Mann-Whitney *U* test. Probabilities of less than 0.05 were statistically significant.

RESULTS

Incidence of MALT lymphoma-associated genetic aberrations

Using a combination of FISH and RT-PCR, 87 cases were of sufficient quality for assessment of the presence of t(11;18)/*API2-MALT1*. Nine t(11;18)/*API2-MALT1*-positive cases were identified by FISH using a *MALT1* break-apart probe and an

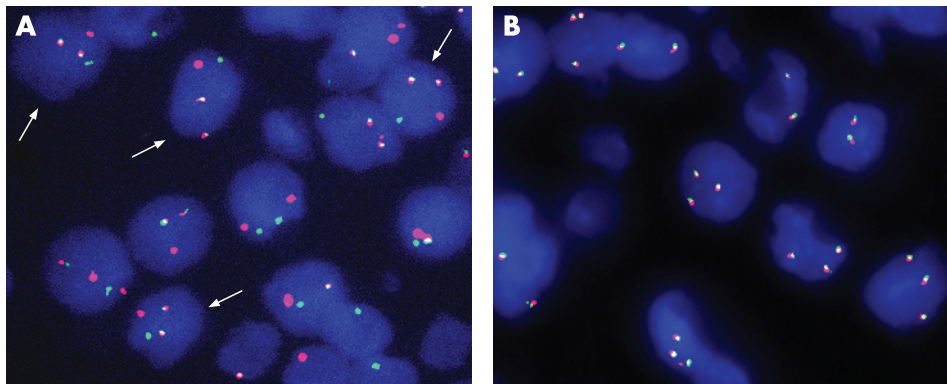


Figure 1 Interphase fluorescence *in situ* hybridisation (FISH) patterns in representative cases. (A) $t(11;18)/API2-MALT1$. FISH with an $API2/MALT1$ dual-colour, dual-fusion translocation probe shows co-localisation of the red and green signals (arrows). (B) Extra copies of $MALT1$. FISH with a $MALT1$ dual-colour break-apart probe demonstrates three or four copies of $MALT1$ gene in 40% of tumour cells.

$API2-MALT1$ dual-colour dual-fusion translocation probe (fig 1A); in all nine cases the presence of $API2-MALT1$ fusion transcripts was also confirmed by RT-PCR. In addition, $API2-MALT1$ fusion transcripts were also identified by RT-PCR in nine cases in which FISH signals were poor. Thus overall, 18 of 87 (21%) cases were positive for $t(11;18)/API2-MALT1$.

Evidence of IGH breakage was found in 4 (6%) of 68 cases in which adequate signals were obtained. The remaining 22 cases showed no signals for FISH with IGH probe. Among the four cases with IGH breakage, one showed $FOXP1$ breakage; the presence of $t(3;14)/FOXP1-IGH$ was confirmed by FISH with a $FOXP1/IGH$ dual-colour, dual-fusion translocation probe. In another case with IGH breakage, $t(14;18)(q32;q21)$ involving IGH and $BCL2$ was detected by FISH with $BCL2$ dual-colour break-apart probe and $IGH/BCL2$ dual-colour, dual-fusion translocation probe; the possibility of follicular lymphoma was excluded by extensive histological and immunohistochemical investigation.²⁴ In the remaining two cases with potential IGH -involved translocations, the partner genes were unknown; neither case showed evidence of a split signal with $MALT1$, $FOXP1$, $BCL10$, $BCL6$, $BCL2$, $CCND1$ or $c-MYC$ dual-colour break-apart probes. None of the cases showed $t(1;14)/BCL10-IGH$ or $t(14;18)/IGH-MALT1$ in the present study. In addition, no cases showed strong Bcl10 nuclear staining as seen in cases with $t(1;14)/BCL10-IGH$.

Extra copies of $MALT1$ (three and occasionally four copies), suggestive of partial or complete trisomy (or occasionally tetrasomy) 18, were detected in 18 (25%) of 71 cases in which adequate signals were obtained (fig 1B). Extra copies of $MALT1$ were not detected in any of the translocation-positive cases, except for one case with a translocation involving IGH and an unknown partner gene. Adequate signals were obtained with the $FOXP1$ dual-colour break-apart probe in 59 of 90 cases, and an extra copy of $FOXP1$ suggestive of partial or complete trisomy 3 was detected in 10 of 59 (17%) cases. None of the 10 cases with an extra copy of $FOXP1$ had a translocation involving $MALT1$ or IGH . Extra copies of both $MALT1$ and $FOXP1$ were observed in 4 of 56 (7%) cases in which adequate signals were observed using both FISH probes. Overall, 24 of 74 (32%) cases contained extra copies of $MALT1$, $FOXP1$ or both. In total, at least 43 of 87 (49%) cases had structural or numerical genetic aberrations.

Relation between genetic aberrations and clinicopathological features

Clinicopathological findings in the $t(11;18)/API2-MALT1$ positive and negative groups are summarised in Supplemental table A. Cases negative for *H pylori* (38% vs 3%) and those not responding to *H pylori* eradication treatment (83% vs 32%) were more frequent in the $t(11;18)/API2-MALT1$ -positive group than in the negative group ($p<0.001$ and $p<0.05$, respectively). Bcl10 nuclear expression as shown by immunohistochemistry

was observed more frequently in the $t(11;18)/API2-MALT1$ -positive group than in the negative group (73% vs 39%, $p<0.05$). Other factors, including depth of tumour invasion, clinical stage, overall CR induction, and disease progression or relapse, did not differ between the two groups.

Clinicopathological findings in the IGH -involved translocation positive and negative groups are also shown in Supplemental table A. No differences were observed between the two groups in any of the factors analysed.

Supplemental table A (available at <http://gut.bmj.com/supplemental>) compares the clinicopathological findings between cases with and without extra copies of $MALT1$ or $FOXP1$. Cases with extra copies of $MALT1$ were older than those without extra copies of $MALT1$ ($p<0.05$). Disease progression or relapse of lymphoma was more frequently observed in cases with extra copies of $MALT1$ than in those without (22% vs 0%, $p<0.005$). Cases with an extra copy of $FOXP1$ had tumours invading the submucosa or beyond more frequently than cases with only two copies (90% vs 55%, $p<0.05$). All other factors, including clinical stage or overall CR induction were not different.

Prognostic impact of genetic aberrations

The follow-up after the diagnosis in 90 patients ranged from 2 to 240 months (mean 65 months). The OS and EFS after 5 years were 88% and 85%, respectively.

Table 1 summarises the results of a univariate analysis for prognosis of patients as assessed by the Kaplan-Meier method with the log-rank test. Cases with macroscopically superficial type tumours showed significantly better OS and EFS (both $p<0.05$). Cases with deeper invasion of the gastric wall showed a significantly worse OS ($p<0.05$), but the difference in EFS was insignificant ($p<0.1$). The presence of extra copies of $MALT1$ was significantly associated with worse EFS ($p<0.005$), although it did not correlate with OS (fig 2A and B). Older patients tended to show worse OS and EFS, and male patients also tended to show worse OS, but these differences were not statistically significant (all $p<0.1$). Other factors, including $t(11;18)/API2-MALT1$, IGH -involved translocations and extra copies of $FOXP1$, did not affect OS or EFS.

The results of a multivariate analysis are shown in table 2. Significant independent prognostic factors for worse OS were deeper invasion of the gastric wall and older age, whereas those for worse EFS were extra copies of $MALT1$ and macroscopic appearance other than superficial type.

DISCUSSION

Although there are a number of publications about the incidence and clinical impact of $t(11;18)/API2-MALT1$ in gastric MALT lymphoma, comprehensive investigation of all MALT lymphoma-associated translocations, including $t(11;18)/API2-MALT1$, $t(1;14)/BCL10-IGH$, $t(14;18)/IGH-MALT1$ and $t(3;14)/$

Table 1 Results of univariate analysis for prognosis evaluated by Kaplan-Meier method

Factors	Overall survival		Event-free survival	
	5 years	p Value*	5 years	p Value*
Age (y)				
≤ 58 or younger (n=39)	0.94	0.072	0.91	0.069
≥ 59 or older (n=51)	0.84		0.79	
Gender				
Male (n=47)	0.82	0.071	0.80	0.197
Female (n=43)	0.95		0.90	
Macroscopic type				
Superficial (n=71)	0.93	0.019	0.90	0.017
Others (n=19)	0.71		0.65	
Depth of tumour invasion				
Mucosa (n=37)	1.00	0.013	0.94	0.083
SM or beyond (n=53)	0.81		0.79	
Clinical stage				
I (n=61)	0.87	0.369	0.83	0.423
II ₁ or more (n=29)	0.92		0.88	
t(11;18)/API2-MALT1				
Positive (n=18)	1.00	0.370	1.00	0.229
Negative (n=69)	0.85		0.80	
IGH-involved translocation				
Positive (n=4)	1.00	0.507	0.75	0.583
Negative (n=64)	0.87		0.84	
Extra copies of MALT1				
Positive (n=18)	0.71	0.144	0.54	0.003
Negative (n=53)	0.89		0.89	
Extra copies of FOXP1				
Positive (n=10)	0.90	0.949	0.79	0.647
Negative (n=49)	0.87		0.83	

FOXP1, forkhead box protein P1; MALT, mucosa-associated lymphoid tissue. *Log-rank test.

FOXP1-IGH, has been carried out in only a few studies.^{4 5 7 8} So far, such a comprehensive study has not been done in Asian cases. In the present study, we investigated the incidence of all the four reported chromosome translocations and of extra copies of *MALT1* and *FOXP1* in Japanese cases of gastric MALT lymphoma.

The reported frequency of t(11;18)/*API2-MALT1* in gastric MALT lymphoma has varied from 5% to 40%.^{4 5 8 11-13 25} Such a variation in frequency among these studies is probably due to bias in case selection^{12 25} or small sample sizes.⁸ In four large studies comprising more than 60 gastric cases, the frequency of t(11;18)/*API2-MALT1* ranged from 15 to 24%,^{4 5 11 13} which was compatible with our present data (21%). All of the four studies and our present one examined a large cohort of unselected cases, and thus the frequency of 20% likely represents its true incidence in gastric MALT lymphoma.

Our present study confirmed that t(11;18)/*API2-MALT1* was significantly associated with *H pylori*-negative cases, resistance to *H pylori* eradication and Bcl10 nuclear expression (Supplemental table A; available at <http://gut.bmj.com/supplemental>), as reported previously.^{12 13 19 25 26} In our study, however, the translocation did not correlate to the clinical stage; this was discordant from several previous studies in which t(11;18)/*API2-MALT1* was

associated with advanced stage MALT lymphoma.^{13 25} The reason for this discrepancy is unclear.

A translocation involving *IGH* was detected in four cases (6%) in our study. Similarly, Remstein *et al*⁸ reported that *IGH*-involved translocations were present in 8% of MALT lymphomas from various organs of patients in North America. In our study, however, none of the cases showed t(1;14)/*BCL10-IGH* or t(14;18)/*IGH-MALT1*. In a large study by Ye *et al*,⁵ t(1;14)/*BCL10-IGH* was detected in 8 of 185 (4%) gastric MALT lymphomas, while three other studies did not detect this translocation in any of the gastric cases examined (n=71, 24 and 22, respectively).^{4 7 8} t(14;18)/*IGH-MALT1* has been found predominantly in extra-gastric MALT lymphoma, whereas gastric cases with this translocation are very rare.^{4 5 8}

In our study, t(3;14)/*FOXP1-IGH* was detected in 1 of 59 (1.7%) cases. This translocation has been occasionally seen in extra-gastric MALT lymphoma and extra-nodal DLBCL.^{6 22 27} Recent data have shown that overexpression of FOXP1 protein is associated with inferior survival in DLBCL²⁸ and MALT lymphoma.⁷ In gastric MALT lymphoma without DLBCL component, t(3;14)/*FOXP1-IGH* has been previously found in only one case in a study from Belgium.²⁷ These observations suggest that t(3;14)/*FOXP1-IGH* rarely occurs in gastric MALT

Table 2 Independent prognostic factors determined by multivariate analysis*

Variables	Coefficient	Standard error	Relative risk	p Value
Overall survival				
Depth of invasion	0.639	0.278	2.294	0.0218
Age	0.073	0.033	2.245	0.0248
Gender	0.956	0.803	1.190	0.2340
Event-free survival				
Extra copies of MALT1	1.448	0.590	2.454	0.0141
Macroscopic type	1.351	0.582	2.321	0.0203
Age	0.046	0.031	1.487	0.1371

*Cox proportional hazards regression model.

lymphoma and such lymphomas may be at risk of poor clinical outcome and/or transformation to DLBCL.⁷

In another case with an *IGH*-involved translocation, we found $t(14;18)/IGH-BCL2$.²⁴ Although $t(14;18)/IGH-BCL2$ is the genetic hallmark of follicular lymphoma, this translocation has also been described in a few cases of MALT lymphoma.²⁹ In the remaining two cases (3%), we could not identify the partner gene for *IGH*. Both the cases were negative for FISH with almost all of the known partner genes. Although $t(6;14)/CCND3-IGH$ has been detected in several cases of DLBCL transformed from MALT lymphoma,³⁰ probes for *CCND3* were not available in our study. Remstein *et al*⁸ also described that 4 of 131 (3%) MALT lymphomas showed translocations involving *IGH* and unknown partner gene. Thus, other as yet undiscovered partner genes for *IGH*-involved translocations are considered to exist among gastric MALT lymphomas. When assessed together in our cohort, *IGH*-involved translocations did not affect any of the clinicopathological features studied, including prognosis (Supplemental table A (available at <http://gut.bmj.com/supplemental>) and table 2); however, cases with this translocation were few and further analyses of a larger number of such translocation-positive cases are warranted.

Aneuploidy, most commonly trisomy 18 and trisomy 3 or both, are frequently observed in $t(11;18)/API2-MALT1$ -negative MALT lymphomas.^{4,9,10,31} We identified extra copies of *MALT1*

and *FOXP1* genes, most likely partial or complete trisomies 18 and 3, in 25% and 17% of cases, respectively. The most important finding in the present study was that the presence of extra copies of *MALT1* was significantly associated with progression or relapse of lymphoma (table 1), and it was an independent prognostic factor for worse event-free survival as determined by Cox multivariate analysis (table 2 and fig 2). Previous studies suggested such numerical gains as trisomies 3 or 18 to be associated with high-grade transformation of MALT lymphoma.^{9,32} Krugmann *et al*³³ reported that trisomy 18q21 (extra copy of *MALT1*) was significantly associated with worse disease-specific survival in 19 cases of gastrointestinal DLBCL with or without MALT lymphoma, although such a difference was not observed among 11 cases of MALT lymphoma studied. In a recent study by Tanimoto *et al*,³⁴ trisomy 18 determined by FISH with a centromere-specific probe was significantly associated with lymphoma recurrence in 34 cases of ocular adnexal MALT lymphoma. Together, these results suggest that partial or complete trisomy 18 may be associated with an adverse clinical course of gastric MALT lymphoma. We thus believe that assessment of copy number of *MALT1*, in addition to other known clinical parameters, is valuable for predicting the clinical course of patients with gastric MALT lymphoma and may help to identify patients for whom closer clinical follow-up is appropriate. However, these findings were based on retrospective studies of cases accrued over relatively long periods and receiving heterogeneous treatment. Therefore, further prospective studies are clearly indicated.

In conclusion, our comprehensive study revealed that $t(11;18)/API2-MALT1$ is frequent, whereas *IGH*-involved translocations are rare in gastric MALT lymphoma in Japan. The presence of extra copies of *MALT1* is a frequent genetic aberration in gastric MALT lymphoma, which appears to predict an adverse clinical course. Further clinical studies of a large number of cases with longer follow up are warranted to clarify whether this numerical change has a major influence on the prognosis of gastric MALT lymphoma.

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Table A can be viewed on the *Gut* website at <http://www.gutjnl.com/supplemental>

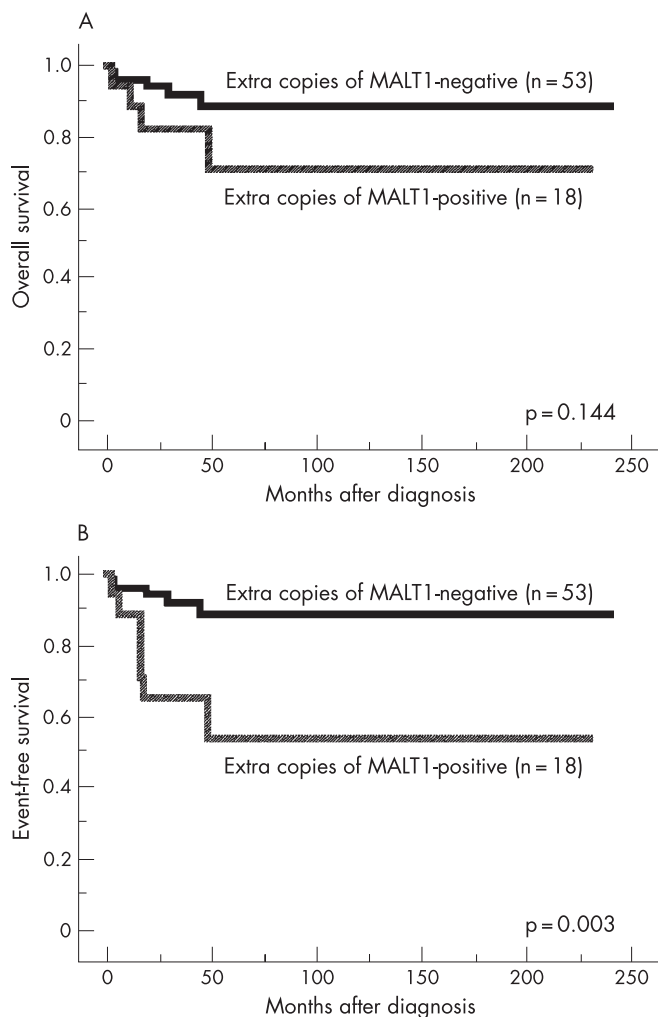


Figure 2 Survival curves of patients of gastric mucosa-associated lymphoid tissue (MALT) lymphoma with (solid line, $n = 18$) and without (dotted line, $n = 53$) extra copies of *MALT1*. (A) Overall survival ($p = 0.144$). (B) Event-free survival ($p = 0.003$).

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