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Gastric MALT lymphoma: Epidemiology and high adenocarcinoma risk in a nation-wide study

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ABSTRACT

Background: Gastric marginal zone non-Hodgkin lymphomas MALT type (gMALT) and gastric adenocarcinomas (GC) are long-term complications of chronic *Helicobacter pylori* gastritis, however, the incidence of gMALT and the GC risk in these patients is unclear.
Objective: To evaluate epidemiological time trends of gMALT in the Netherlands and to estimate GC risk.
Methods: Patients with a first diagnosis of gMALT between 1991 and 2006 were identified in the Dutch nation-wide histopathology registry (PALGA). Age-standardised incidence rates were calculated. The incidences of GC in patients with gMALT and in the Dutch population were compared. Relative risks were calculated by a Poisson Model.
Results: In total, 1419 patients were newly diagnosed with gMALT, compatible with an incidence of 0.41/100,000/year. GC was diagnosed in 34 (2.4%) patients of the cohort. Patients with gMALT had a sixfold increased risk for GC in comparison with the general population ($p < 0.001$). This risk was 16.6 times higher in gMALT patients aged between 45 and 59 years than in the Dutch population ($p < 0.001$).
Conclusions: GC risk in patients with gMALT is six times higher than in the Dutch population and warrants accurate re-evaluation after diagnosis and treatment for gMALT.

1. Introduction

Helicobacter pylori causes chronic inflammation of the gastric mucosa in virtually all infected subjects. This inflammatory process can progress through the pre-malignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinomas.[1,2] As such, *H. pylori* infection is the most important risk factor for the development of gastric adenocarcinomas. Although, the incidence of gastric cancer is declining in the Western world, gastric cancer remains the 4th most common cancer and second leading cause of cancer-related death worldwide.[3,4] The declining incidence of gastric cancer in Western countries is similar to the declining incidence of peptic ulcer disease, attributed to the declining *H. pylori* prevalence.[5,6]

In addition, *H. pylori* infection has increasingly been recognised in the pathogenesis of gastric mucosa-associated lymphoid tissue lymphomas (gMALT).[7,8] Although gMALTs are

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also strongly associated with *H. pylori* infection, the incidence of this condition has, in contrast to the gastric cancer incidence, been reported to increase.[8–12] It is controversial whether this is a true increase with a shift in outcomes of *H. pylori* infection. Alternatively, changes in the number of endoscopic procedures, biopsy sampling protocols and histological criteria could have influenced the number of diagnoses.[12] Progression of low-grade gMALT is slow, and *H. pylori* eradication alone leads to partial or complete remission in 60–80% of patients, in particular those without a specific *API2-MALT1* *t*(11;18) chromosomal translocation.[2,13] On the contrary, gastric cancer is usually diagnosed at an advanced stage with only limited curative options and consequently a low 5-year survival rate. Although both conditions are long-term complications of chronic *H. pylori* infection, the potential interrelation is unclear and it is controversial whether gastric cancer risk is increased in patients with gMALT. Previous case series and small cohort studies described the occurrence of adenocarcinomas simultaneously or during follow-up of gMALT,[14–18] however, other studies could not confirm these observations.[11,19–21] In addition, a recent study observed increased progression of pre-malignant gastric lesions in patients with gMALT as compared to patients with non-complicated gastritis.[13] On the basis of these contrasting data and in the absence of long-term data in larger cohorts, the risk for gastric cancer in patients with gMALT remains unclear.

Therefore, the aim of this study was to evaluate epidemiological time trends of gMALT in the Netherlands and to evaluate gastric cancer risk in patients with a diagnosis of gMALT.

2. Methods

2.1. Histopathology database

In the Netherlands, all histopathology and cytopathology reports are collected in a national archive (PALGA database), which has nation-wide coverage since 1991.[22] Patients in this database are identified by date of birth, gender and the first four characters of their family name. Though sometimes identities of two patients are falsely matched, this identification string enables the linkage of different tests belonging to the same patient, and therefore also to follow individual testing histories (dates and diagnoses) irrespective of the facility of treatment.[23]

All specimens receive a diagnostic code, similar to the Systematised Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists.[24] This code consists of a term indicating the anatomical location, type of sample and a morphological term describing the finding. The records in the database contain these codes and the summary of the pathology report. In this study, data recorded in the PALGA database between 1991 and 2006 were included. For each report, gender, date of birth, date of pathology report, summary text and diagnostic codes were made available.

2.2. Patient selection

All patients with a histologically confirmed diagnosis of gMALT were identified in the database. The diagnostic codes that were used to identify the patients with gMALT are described in Appendix. To evaluate the incidence of gMALT in different age classes, incidence numbers in different periods were calculated within the 5-year age groups. The ratio of the number of new patients with a positive biopsy for gMALT to the number of new patients with a first time gastric biopsy was calculated, in order to correct for possible changes in frequency of upper gastro-intestinal endoscopies with biopsy sampling.

Within the cohort of patients with a gMALT, all patients with a histologically confirmed diagnosis of gastric cancer were identified. Timing of gastric cancer diagnosis was evaluated with regard to diagnosis of gMALT. In this evaluation, patients with a gastric cancer diagnosis simultaneously with, or within one year prior to or after diagnosis of gMALT were considered concomitant diagnoses.

In addition, all patients with a diagnosis of atrophic gastritis, intestinal metaplasia or dysplasia prior to, simultaneous with, or after the diagnosis of gMALT were identified.

2.3. Statistical analysis

Age-standardised incidence rates (World standardised rate, WSR) of histologically confirmed gMALT were evaluated for the study period. To compare categorical and continuous variables between patients with low, intermediate to high and undefined grade gMALT, χ^2-tests, *t*-tests and one way ANOVA tests were used, considering a two-sided *p*-value <0.05 as statistically significant.

To calculate the relative risk of gastric cancer in patients with gMALT, the incidence of gastric cancer observed in patients with gMALT was compared to the incidence of gastric cancers in the general Dutch population from 1991 to 2006 and aggregated over age and sex. As the PALGA registry does not contain date of death of patients, unless an autopsy had been performed, the person-years at risk would be overestimated. Therefore, we imputed death to get a correct estimate of the number of person-years at risk for all patients that did not develop gastric cancer during follow-up. Starting from the calendar year, age and gender of the persons, we collected the survival data from the general Dutch population for ever open-ended follow-up. Drawing from a binomial distribution for every year then yielded a dataset with an approximately unbiased number of years-at-risk. The number of patients is large, but we tried multiple imputation, that did not change the results, as was to be expected. The incidence of gastric cancer in the Dutch population was calculated on the basis of the total number of gastric cancers registered in the PALGA database and the midyear Dutch population.[25] A Poisson Model, corrected for age categories, gender and calendar year, was used for calculating the relative risks and 95% confidence intervals (CIs).

3. Results

Between 1991 and 2006, 1419 patients were newly diagnosed with gMALT, 972 patients were initially diagnosed with a low-grade lymphoma, 357 patients with an intermediate to

high-grade lymphoma and in 90 patients the grade of the lymphoma was undefined (Table 1). Within the group of patients with a low-grade lymphoma, 32 (3.3%) patients developed a high-grade lymphoma within 1 to 8 years.

3.1. *Epidemiology*

Overall, the mean age of patients at diagnosis of gMALT was 66.1 (SD 14.1) years (range 13.7–98.2 years), and the peak incidence of gMALT both in men and women was between 70 and 74 years (Fig. 1). The proportion of male to female patients in the cohort was 51.9 to 48.1% (Table 1). No significant differences in male to female ratios were observed between patients with low-grade, intermediate to high-grade or undefined grade gMALT ($p = 0.78$). Patients with an initial diagnosis of low-grade gMALT (median age 67.0 years) were significantly younger compared to patients with intermediate to high-grade gMALT (median age 70.6 years) ($p = 0.002$). Age at diagnosis was significantly higher in females as compared to males, both in patients with low-grade gMALT ($p = 0.03$) and intermediate to high-grade gMALT ($p = 0.001$).

Over the whole study period, the average number of new diagnoses of gMALT was 88.7 cases per year, and the age standardised incidence rate was 0.41 per 100,000 per year (WSR) (Fig. 2). This incidence was not stable over the total study period. At first, the incidence of gMALT increased with 5.8% (95% CI 1.9–9.9%) per year in the period from 1991 to 1997. This was followed by an annual 8.8% (95% CI 6.2–11.4%) decline until 2006 (Fig. 2). Altogether, this corresponded with an annual WSR of 0.28 per 100,000 in 1991, increasing to a maximum of 0.72 in 1997, followed by a decrease to 0.27 in 2006. Gastric MALT lymphoma was diagnosed significantly more often in the period from 1991 to 2000 as compared to the period from 2001 to 2006 ($p < 0.001$).

3.2. *Gastric cancer risk*

In total, 34 (2.4%) gMALT patients (18 males, 16 females) were diagnosed with gastric cancer at a median age of 72.0 years (SD 9.6). This comprised 2.7% of 1244 patients in whom no gastrectomy was performed after diagnosis of gMALT. Gastric cancer was diagnosed prior to the diagnosis of gMALT in 3 (8.8%) patients, in 18 (52.9%) patients both malignancies were diagnosed simultaneously (i.e. within a time frame of one year), and in 13 (38.2%) patients gastric cancer was diagnosed more than one year after the gMALT diagnosis (Table 2). The median interval between gastric cancer and gMALT in patients with gastric cancer development after diagnosis of gMALT was 6.0 (range 1.1–7.4) years.

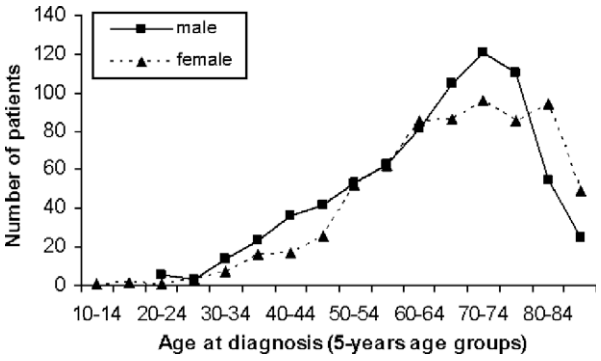

Fig. 1 – Age at gastric MALT lymphoma diagnosis.

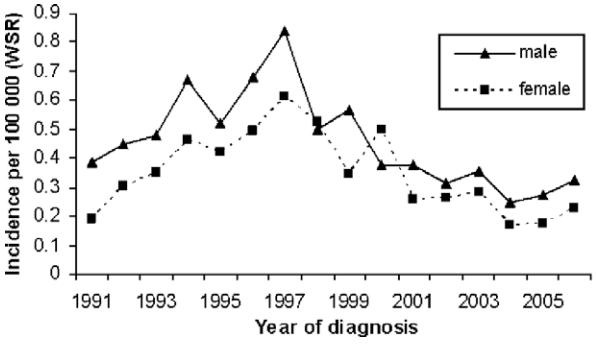

Fig. 2 – The incidence of gastric MALT lymphoma (WSR, World standardised rate) in the Netherlands.

Details on stage of gastric cancer were provided in 15 (44%) patients. Five (15%) patients were diagnosed at a stage of early gastric cancer, however, in 10 (29.4%) patients the tumour was already invading the lamina propria, submucosa or beyond. In addition, lymph nodes were involved in 4 (11.8%) patients, as demonstrated by histological evaluation after gastric resection.

Overall, the study population contained 440 (31%) patients with a diagnosis of a pre-malignant gastric lesion prior to, simultaneously with, or after the diagnosis of gMALT, of which 65 (4.6%) patients were diagnosed with atrophic gastritis, 302 (21.3%) patients with intestinal metaplasia and 73 (5.1%) patients with dysplasia. In 21% of these patients a diagnosis of atrophic gastritis, intestinal metaplasia or dysplasia preceded the diagnosis of gastric cancer.

Gastric cancer risk was not significantly different between patients with low, intermediate to high or undefined grade gMALT ($p = 0.21$). In addition, no significant differences in

Table 1 – Baseline characteristics

	Total	Low-grade	Intermediate to high grade	Undefined grade
Number of patients with gastric MALT lymphoma	1419	972 (68.5%)	357 (25.2%)	90(6.3%)
Male/Female (%)	51.9/48.1	51.3/48.7	53.5/46.5	52.2/47.8
Age				
Median (years)	68.0	67.0	70.6	68.7
Percentile 25th and 75th	57.6/76.7	57.1/75.4	58.9/78.7	57.1/76.2

Table 2 – Gastric MALT lymphoma and gastric cancer diagnosis

	Total	Low-grade	Intermediate to high grade	Undefined grade
Timing of gastric cancer diagnosis				
Prior to MALT lymphoma (%)	3(8.8)	3(10.7)	0	0
Concomitant with MALT lymphoma (%)	18(52.9)	16(57.1)	1(20.0)	1(100)
After MALT lymphoma (%)	13(38.2)	9(32.1)	4(80.0)	0
Male/Female (%)	52.9/47.1	60.7/39.3	20.0/80.0	0/100
Age				
Median (years)	72.0	73.2	70.2	72.2
Percentile 25th and 75th	65.5/78.7	64.2/78.2	61.0/86.9	

Table 3 – The relative risk of gastric cancer (GC) in patients with gastric MALT lymphoma (gMALT) as compared to the general Dutch population

		GC in Dutch population	GC in gMALT patients	Relative risk	95%CI	*P*-value for difference
Overall		36,577	30	6.11	[4.28–8.72]	
Sex	Male	22,778	15	4.39	[2.65–7.28]	0.02
	Female	13,799	15	10.04	[6.07–16.60]	
Age at baseline	45–59 years	6229	5	16.64	[5.45–50.80]	0.004
	60–74 years	15,253	17	10.64	[6.52–17.4]	
	⩾75 years	13,666	8	3.43	[1.91–6.13]	

gastric cancer risk were demonstrated between male and female patients ($p = 0.91$).

Overall, patients with a diagnosis of gMALT were at a six times higher risk of developing gastric cancer as compared to the general Dutch population (Table 3). Males with gMALT had a 4.4 times higher risk as compared to the general population ($p < 0.001$), whereas females had a 10.0 times higher risk ($p < 0.001$). The relative risk of gastric cancer was significantly higher in female patients with a gMALT as compared to male patients ($p = 0.02$). However, the absolute risk of gastric cancer for males and females older than 45 years was not significantly different (respectively, 4.0/1000 person-years and 4.3/1000 person-years; $p = 0.81$). Gastric cancer risk was 16.6 times increased in patients aged between 45 and 59 years as compared to the general Dutch population ($p < 0.001$), 10-fold increased in patients aged between 60 years and 74 years and threefold increased in those above 74 years (Table 3). These differences in relative risk for the age groups were significant ($p = 0.004$). However, the absolute gastric cancer risk in patients with gMALT did not differ between those aged 45 to 59 years and those above 59 years ($p = 0.07$).

4. Discussion

First of all this study provides long-term nation-wide data on the incidence of gMALT in a Western population. It shows an overall incidence of gMALT of approximately 0.4/100,000/year. Secondly, our data show that this incidence has considerably changed over the past 18 years, initially increasing between 1991 and 1997, which was followed by a rapid decline. Thirdly, we provide long-term data that confirm the suggestion from previous case reports that gMALT patients have a considerably higher gastric cancer risk than the general population. In most cases, gastric cancer is diagnosed within one year prior to or after the diagnosis of gMALT. Therefore, on the basis of our data, accurate evaluation of gMALT seems to be warranted for a diagnosis of gastric cancer concomitantly or after the diagnosis of gMALT.

Our data demonstrate that gMALT is a relatively rare disease in a Western population. Previous studies in Western countries have demonstrated incidences varying between 0.21/100,000 (England) and 13/100,000 (Italy).[2,26,27] These differences are probably explained by differences in the prevalence of *H. pylori* between the studied populations, study power based on the magnitude of the study population, the period of follow-up and the timing of the study.[2,26,28] In our population, a diagnosis of gMALT was not extremely rare as approximately 0.2% of the total number of patients with a first gastric biopsy over the study period were diagnosed with a gMALT.

Previous studies described an increasing incidence of gastric lymphomas in contrast to the declining incidences of *H. pylori* infection, peptic ulcer disease, atrophic gastritis, intestinal metaplasia and gastric adenocarcinomas.[5,6,12] Our data similarly demonstrate that the incidence of gMALT increased from 1991 to 1997, but decreased rather rapidly thereafter. The initial increase is probably related to the increasing interest in this diagnosis after the discovery of an association between *H. pylori* infection and gMALT in 1991.[8] The importance of *H. pylori* as risk factor for MALT lymphoma was confirmed by the regression of low-grade MALT lymphoma after *H. pylori* eradication.[19,29] Thereby, gMALT became an infection-associated malignant disease.[2] This led in a change of primary treatment strategy from chemoradiotherapy and surgery to *H. pylori* eradication therapy. This major change may have contributed to an increase in the number

of new cases diagnosed with gMALT during those years. Furthermore, improved endoscopic and histological diagnostic procedures may also have contributed to the increasing incidence of gMALTs.[30–32] For several years, all non-Hodgkin lymphomas (NHLs) were classified following the Working Formulation (WF) in low-grade and high-grade lymphomas. This working formulation did not include several morphologic and clinical distinct entities, including gMALT. Consensus for a more multifaceted approach to NHLs was reached in a revised European–American lymphoma (REAL) classification in 1993, which recognised the mucosa-associated lymphomas.[33] Thereafter, gMALTs were considered a specific entity.[2] Currently their incidence is rapidly declining. This decline is likely in part related to the current decline in the prevalence of *H. pylori* in Western countries. However, the decline of incidence of gMALT is much more rapid than the declining *H. pylori* prevalence.[5,34,35] Therefore, other factors must additionally play a role and need to be further investigated.

Although several case series were published on synchronous and metachronous occurrence of both gastric cancer and gMALT, it remained unclear whether gastric cancer risk was increased in gMALT patients compared to the general population.[11,14,16,19,36–38] Our study demonstrates this risk is indeed about six times increased (Table 3). The absolute risk was equal in male and female gMALT patients, which contrasts with the general population, where the risk for gastric cancer is considerably higher in men. Thus, the relative risk of gastric cancer in MALT patients is higher in women than in men. Similarly, the gastric cancer risk was the same in younger and elderly gMALT patients, and thus the relative risk for gastric cancer was significantly higher in younger MALT lymphoma patients (Table 3). The relative risks of gastric cancer after a diagnosis of gMALT described in our study could even be higher since gastrectomy was performed in 175 patients after diagnosis of a gMALT, in particular in the early years when *H. pylori* eradication was not yet an accepted treatment method.

As patients with gastric MALT lymphoma are already at an increased risk of developing gastric cancer by being *H. pylori* positive, a further comparison between *H. pylori*-positive subgroups is essential. Previous studies demonstrated that *H. pylori* infection increased gastric cancer risk at least twofold resulting for *H. pylori*-positives in an estimated lifetime risk for gastric cancer of approximately 1%.[39,40] In addition, we recently published a study describing the risk of gastric cancer in a large cohort of patients with atrophic gastritis and intestinal metaplasia, which occurs like MALT lymphoma against a background of *H. pylori* infection. This study demonstrated that within ten years of follow-up the gastric cancer risk in these subjects with a pre-neoplastic condition varied between the two and three percent.[41] This background supports the conclusion that patients with gMALT are at increased risk for gastric cancer compared to *H. pylori*-positive subjects, and that this risk is in fact very similar to patients with atrophic gastritis and intestinal metaplasia.[41]

In 38% of patients with diagnosis of gastric cancer, gastric cancer was diagnosed after gMALT with a median interval of 6.0 years (range1–7). This interval is similar to the interval observed in a review of previous cases on metachronous occurrence of gMALT which reported 6 months to 5 years.[16] However, the exact period between diagnosis of a gMALT and cancer or remission is difficult to interpret, since different histological scoring systems have been used to evaluate lymphoma response to therapy over the past decade.[29,42] As these grading systems demonstrated low interobserver reproducibility, a new grading system based on evaluation of diagnostic features of lymphoepithelial changes was put forward.[43] According to this grading system, a recent study described a favourable disease course of patients treated with *H. pylori* eradication, after 42.2 months of follow-up, in which one-third of the patients went into complete remission.[21,43] However, the findings in our study emphasise the need of accurate endoscopic and histological re-evaluation of the gastric mucosa after diagnosis of a gMALT, since the majority who developed gastric cancer was diagnosed with adenocarcinoma concomitantly (52.9%) with their gMALT or during later surveillance (38.2%).

Although this study describes a large nation-wide cohort of patients with gMALT with long-term follow-up, potential limitations of this study warrant consideration.

Firstly, for most of the period under study, MALT lymphomas were classified as either low- or high-grade and it is therefore that our report included cases under these search terms. At present, gMALTs are considered as a specific disease entity of marginal zone lymphoma (mucosa-associated lymphoid tissue lymphoma (MALT) type), which led to the formalised WHO classification, according to which these lesions are now referred to as gastric marginal zone lymphomas MALT type.[44] Also, the term high-grade MALT lymphoma was replaced by Diffuse Large B-Cell Lymphoma (DLBCL) in this new classification, as it was discovered that low-grade and high-grade gMALTs have a different histogenesis.[44] These DLBCLs may contain a low-grade MALT lymphoma component. However, it remains unclear to which extent they transformed from low-grade MALT lymphomas *versus de novo* DLBCLs.[45] For these reasons, it is likely that a small proportion of the high-grade gastric MALT lymphomas in our cohort included DLBCLs unrelated to MALT. However, these changes of nomenclature have not led to a major change in diagnoses and therefore unlikely affected the main outcome parameters of our study, i.e. the incidence of gMALTs and the risk for gastric cancer in these patients. Secondly, we could not evaluate the extension of pre-malignant gastric lesions in the mucosa surrounding the MALT lymphomas, as the relatively low percentage of patients with gastric atrophy, intestinal metaplasia and dysplasia prior to or simultaneous with gMALT diagnosis made this impossible. In addition, details on location and invasion of the MALT lymphomas were not provided. Lymphomas tend to occur proximally in the stomach, whereas gastric adenocarcinomas occur more distal.[36] For these reasons, details on extension of pre-malignant gastric lesion, and size and depth of MALT lymphoma might identify patients at higher risk and consequently lead to more accurate surveillance. Similarly, evaluating the gastric cancer risk in the cohort after stratification by *H. pylori* and translocation status may also result in more accurate surveillance and prognosis. Previous studies observed the specific *API2-MALT1* t(11;18) chromosomal translocation in approximately 30% (range 18–40%) of gMALT patients.[2,46,47] Most patients with this specific translocation do not respond to *H. pylori*

eradication and demonstrate dissemination to regional lymph nodes or distal sites than the stomach more frequently. Development of gastric cancer was reported to occur in translocation-positive patients. However, these case series were very small and the exact risk of developing gastric cancer remained unclear.[48,49] For these reasons, a large prospective study of patients with gMALT and determination of their translocation status is essential to evaluate patients at high risk of developing gastric cancer, however, the rare appearance of gMALTs will make this study hardly feasible. Thirdly, as limited numbers of biopsies can provide insufficient information for subtyping, and determination of horizontal extension and multifocality of gMALTs, previous studies described the need for a standardised protocol taking 20–30 biopsies from involved and uninvolved mucosa both at baseline and during follow-up.[32,50] However, we could not evaluate the number and distribution of biopsies obtained within each individual case and at every time point. Therefore, the number of patients with in particular pre-malignant gastric lesions after a diagnosis of gMALT may have been overdiagnosed.[51] Finally, a previous study proposed that gMALT patients treated with chemo- and/or radiotherapy were particularly at increased risk for gastric cancer,[52] but we were unable to assess this in our study population as we lack details with respect to chemoradiotherapy that without doubt has been given to patients during the first years of our study period.

In conclusion, the overall incidence of gMALT is low and currently declining, which is likely related to the current decline in the prevalence of *H. pylori* infections, but also has to be due to other unidentified factors as the decline is considerably more rapid than the decline of *H. pylori* prevalence. After a diagnosis of gMALT, an accurate endoscopic and histological re-evaluation of the gastric mucosa seem to be warranted as gastric cancer risk in patients with gMALT is substantial and the majority who develop gastric cancer are diagnosed concomitantly or after their gMALT. Future research is needed to clarify the clinical course of these patients in order to improve treatment and prognosis of patients with gMALT.

Conflict of interest statement

None declared.

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Appendix A

The following SNOMED-like codes were used:

- *Stomach*: T63000.
- *Atrophic gastritis*: M58000, M58001, M58010.
- *Intestinal metaplasia*: M73000, M73200, M73320, M73321, M73300.
- *Dysplasia*: M74000, M74006, M74007, M74008, M74009.
- *Gastric cancer*: M81403, M80103, M84803, M81443, M81453, M84903, M82113, M80503, M82603, M69360, M81404, M80104, M80105, M80123, M80193, M80213, M80203.
- *MALT lymphoma*: M97153, M97183, M97163, M96993, M97183.
- *Malignant lymphoma/malignant non-Hodgkin lymfoma*: M95903, F40640.

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