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

L.G. Capelle^{a,*}, A.C. de Vries^a, C.W.N. Looman^b, M.K. Casparie^c, H. Boot^d, G.A. Meijer^e, E.J. Kuipers^a

^aDepartment of Gastroenterology and Hepatology, Erasmus University Medical Center, Room L-462, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

^bPublic Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands

^cStichting PALGA, The Netherlands

^dDepartment of Gastroenterology, Antoni van Leeuwenhoek Hospital, Netherlands Cancer Institute, Amsterdam, The Netherlands

^eDepartment of Pathology, VU University Medical Center, Amsterdam, The Netherlands

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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.

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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

* Corresponding author. Tel.: +31 (0) 107034545; fax: +31 (0) 107032793.

E-mail address: L.Capelle@erasmusmc.nl (L.G. Capelle).

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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

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