Original Article

Gastric Cancer in Thai Patients, *Helicobacter pylori* and Human Epidermal Growth Factor Receptor 2 (HER2) Status

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Background: Gastric cancer is a common cancer with high burden of disease in many countries including Thailand.

Objective: The presented study is to determine current status of gastric cancer in Thai patients in various aspects.

Materials and Methods: The authors retrospectively reviewed the records of 68 patients diagnosed with histologically proven gastric cancer in King Chulalongkorn Memorial Hospital from 2012 to 2016.

Results: There were 36 males and 32 females with the mean age at 63.3±13.1 years. The most common initial symptoms were abdominal pain in females and gastrointestinal bleeding in males. Adenocarcinoma was the most common pathological finding. 16 of 34 patients had positive *Helicobacter pylori* testing and 3 of 14 patients had HER2-positive cancer. The percentage of patients with advanced-stage cancer was not significantly different between positive and negative groups of *Helicobacter pylori,* HER2, smoking, alcohol drinking and also between sexes. The majority of adenocarcinoma was stage IV in 51.6% with poorly-differentiated grading in 64.5%. The mean age of patients with metastasis was significantly lower than that of patients who did not. Surgical resection was the primary treatment.

Conclusion: Gastric cancer is still considered to be a health problem in Thailand with delayed diagnosis. Early diagnosis and prompt treatment should be encouraged.

Keywords: Gastric cancer, *Helicobacter pylori*, Thailand, Stomach cancer

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Gastric cancer is the fifth most commonly diagnosed cancer in the world with the incidence of almost 1 million cases per year. The total death was about 723,000 cases per year which was the third most common cause of cancer-related death worldwide following lung and liver cancer[1]. Recent study demonstrated that incidence was highest in Eastern Asian and South American countries and lowest in South Western Asia, Western European and Oceania countries. Although most countries had favorable decreasing trends in incidence rate, burden of gastric cancer remains high in many countries including Thailand[2].

Helicobacter pylori (*H. pylori*) and diet were considered to be the most important etiologic risk factors of gastric cancer. Colonization of *H. pylori* at gastric mucosa can induce inflammatory reaction and lead to precancerous mucosal metaplasia and dysplasia. High salt intake, dried fish and meat, pickled or smoked foods, and refined carbohydrates were significantly associated with increased risk[3]. The favorable trends of gastric cancer in most countries may be caused by lifestyle modification and decreased prevalence of *H. pylori*[2].

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine-kinase receptor that regulates cell proliferation, differentiation, and survival. HER2-positive gastric cancer was reported to associate with poor prognosis, increased aggressiveness of disease and shorten survival[4].

According to previous literature conducted in Thai patients from 1994 to 1998, gastric cancer was considered to be an important health problem with a poor prognosis in Thailand[5].

The objective of the present study is to collect data of gastric cancer in Thai patients and analyze a current status of this disease in various aspects including *H. pylori* and HER2 status. The authors also aimed to find any changes of current status of gastric cancer compared to previous studies.

Materials and Methods

Patients

The presented study, which was carried out in compliance with the international guidelines for human

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research protection as Declaration of Helsinki, was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The authors retrospectively reviewed the medical records of patients who were diagnosed with gastric cancer in King Chulalongkorn Memorial Hospital, Bangkok, Thailand during the 5-year period from January 2012 to December 2016. The diagnosis of gastric cancer was characterized by diagnosis of malignant neoplasm of stomach, C16.0 to C16.9 in ICD-10 diagnosis code system, combined with proven histological finding of gastric cancer.

Data collection

The medical records were reviewed and analyzed clinical information including sex, age, chief complaint, onset of symptom, alcohol drinking and smoking history, TNM staging and treatment. Locations of tumor were assessed by endoscopic reports. Pathology and immunohistochemistry results, from either endoscopic biopsy or surgical specimen, were reviewed for pathologic type and grading of tumor. HER2 status of surgical specimen was detected by immunohistochemistry method. Additionally, *H. pylori* testing was done in some patients by rapid urease test, from either endoscopic biopsy or surgical specimen, and/or urea breath test method.

Statistical analysis

IBM SPSS Statistics version 23 was used for analysis of patient characteristics with descriptive statistics. The data were presented as mean and standard deviation (SD). Independent t-test was used to assess differences of quantitative data between 2 groups and Chi-square or Fisher's exact test was used to determine statistical differences between groups of categorical data. Statistical significance was defined as *p*-value below 0.05.

Results

Firstly, 388 patients who were diagnosed with malignant neoplasm of stomach, C16.0 to C16.9 in ICD-10 diagnosis code system from hospital database over the 5-year period were enrolled. Then histological reports of these patients were reviewed, and 89 patients who were diagnosed with histologically proven gastric cancer were recruited. However, 21 patients of this group were excluded due to incomplete clinical information.

Demographic data and presentations

Among 68 patients, there were 36 males (52.9%) and 32 females (47.1%). Age of this group ranged from 37 to 86 years old with the mean age of 63.3±13.1 years (Figure 1). The average duration prior to first presentation was 16 weeks. The 2 most common bringing patients to the hospital were abdominal pain (45.6%) and gastrointestinal bleeding (29.4%) (Table 1). Female mostly had abdominal pain as the first clinical presentation which was significantly higher than male (65.6% vs. 27.8%, odds ratio (OR) 4.964, $p = 0.002$, 95% CI 1.769 to 13.925). While the most common initial symptom of male was upper gastrointestinal bleeding, however, there was no significance between male and female (38.9% vs. 18.8%, OR 2.758, $p = 0.069$, 95% CI 0.907 to 8.386) (Figure 2). Adenocarcinoma was the most common pathological finding (91.2%), followed by lymphoma (2.9%), metastatic melanoma, adenosquamous carcinoma, pleomorphic sarcoma and uncategorized carcinoma (1.1% each). The lesions mostly located at proximal part (fundus and cardia) in 48.5%, followed by distal part (body, pylorus and antrum) in 47.1% and diffuse part in 4.4%.

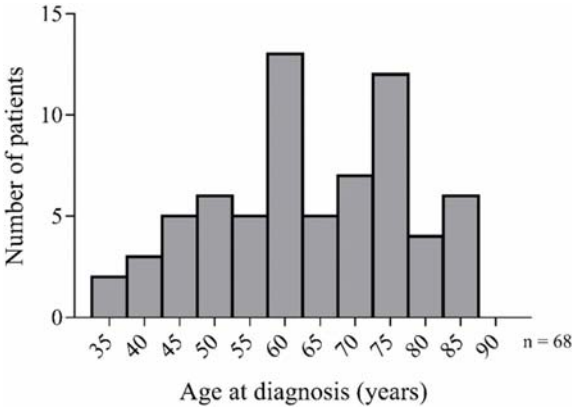

Figure 1. Histogram of age of gastric cancer patients.

Table 1. Presenting symptoms of 68 patients with gastric cancer

Presenting symptoms	n (%)
Abdominal pain	31 (45.6)
Gastrointestinal bleeding	20 (29.4)
Vomiting	5 (7.4)
Fatigue	5 (7.4)
Abdominal mass	4 (5.9)
Accidental finding	2 (3.0)
Weight loss	1 (1.5)

H. pylori status

H. pylori testing was done in 34 patients with rapid urease test and/or urea breath test. There were 16 patients (47.1%) with positive result. The percentage of patients with advanced stage cancer (stage II, III and IV) in positive result group was not significantly different from negative result group (80% vs. 66.7%, $p = 0.458$).

HER2 status

HER2 test was examined in 14 patients; there were 3 patients (21.4%) with positive result. Patients with advanced stage cancer in HER2-positive group was not significantly different from HER2-negative group (100% of HER2-positive group and 88.9% of HER2-negative group, $p = 1.000$).

Gastric adenocarcinoma

Regarding adenocarcinoma group, there were 39.7% and 23.5% of patients who smoked or drank alcohol, respectively.The percentage of patients with advanced stage cancer in smoking group was not significantly different from non-smoking group (88.9% vs. 80.6%, p = 0.639). The percentage of patients with advanced stage cancer in alcoholic group was also not significantly different from non-alcoholic group (100% vs. 78.3%, p = 0.123). Tumor staging according to the TMN classification was as follows: 10 patients (16.1%) were classified as stage I, 8 patients (12.9%) as stage II, 11 patients (17.7%) as stage III, 32 patients (51.6%) as stage IV, and 1 patient (1.6%) of this group was unknown in staging. The percentage of advanced stage of adenocarcinoma at first diagnosis was not significantly different between male and female (83.3% of males and 86.2% of females, OR 1.250, p = 0.750, 95% CI 0.317 to 4.929). Among adenocarcinoma group, 21 patients (33.9%) had distant metastasis. The mean age of patients who had metastasis was significantly lower than that of patients who did not (58.0±13.2 and 66.9±13.3, p = 0.024) (Figure 3). There were 4 patients (4.4%) who were younger than 40 years old. Three of 4 patients (75%) had poorly-differentiated adenocarcinoma. Another patient had moderately-differentiated adenocarcinoma with stage IV classification. With regard to grading, there were 64.5% poorly-differentiated, 16.1% moderately-differentiated, 14.5% well-differentiated grade and 4.8% missing data. Poorly differentiated adenocarcinoma was the most common pathologic grading in both sexes, and the percentage of females with poorly-differentiated adenocarcinoma was significantly higher than those of males (82.8% vs. 53.3%, odds ratio 4.2, 95% CI 1.264 to 13.961, p = 0.016) (Figure 4).

Treatments

Concerning management of adenocarcinoma, surgical resection was the primary treatment. There were 39 patients (62.9%) of this group who underwent definite surgery which was defined as either total gastrectomy, subtotal gastrectomy or extensive gastrectomy. Types of surgery depended on location and extension of tumor. Thirty-two patients (51.6%) of the cases received systemic chemotherapy in concomitant with surgery and 11 patients (17.7%) were given systemic chemotherapy alone as a single treatment. Types of treatment correlated with staging of tumor and metastasis.

Discussion

Gastric cancer is usually found in middle to old-aged group like many other types of cancer. Male gastric cancer incidence rates were higher than female rates regardless of countries. The lower incidence rate of gastric cancer among female than male may result from lower exposure to some risk factors such as cigarette smoking and heavy alcohol drinking. However, several countries including Thailand had similar incidence rate between male and female which was consistent with the presented finding. The pathophysiological explanation of such finding remains unclear but may implicate

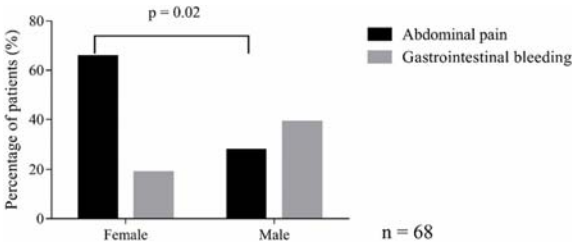

Figure 2. Percentage of patients presenting with abdominal pain and gastrointestinal bleeding categorized by gender.

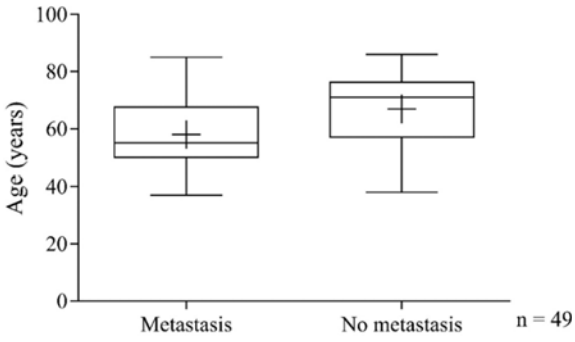

Figure 3. Box whisker plots (2.5 to 97.2 percentile) showing age of patients with and without metastasis.

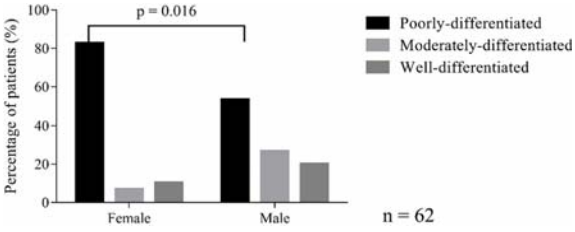

Figure 4. Percentage of patients with poorly-, moderately- and well-differentiated adenocarcinoma categorized by gender.

that there are some unidentified risk factors[2]. Even though gastric cancer is a disease of middle to old age, the data presented that metastasis was significantly correlated with younger age in adenocarcinoma group. The study of gastric cancer in Thai patients in 1994 to 1998 also reported that approximately one-fifth in their series were younger than 40 years old and tended to have distant metastasis[5]. Many studies proposed that gastric cancer in young patient is associated with poorer prognosis. There was a prospective study reported that 50% of young gastric cancer patient presented in stage IV and none of them presented as stage I[6]. However, there was a study which suggested that overall survival was not significantly different among the age groups, but metastatic disease at diagnosis was the only factor

associated with a poorer prognosis in young adult[7]. One possible reason may be delayed diagnosis due to misunderstanding of natural history of disease. Physicians should keep in mind that gastric cancer can occur in patients at any age groups and in various presentations, therefore healthcare workers should place an emphasis on early detection and prompt treatment.

The 2 most common complaints of patients with gastric cancer were abdominal pain and upper gastrointestinal bleeding. Interestingly, the result of this study showed that the most frequent initial symptom in males was upper gastrointestinal bleeding, whereas females commonly presented with abdominal pain as the first complaint. There were several supportive literatures showing that incidence of acute upper gastrointestinal bleeding was prominently higher in males[8]. Since alcohol was associated with increased risk of upper gastrointestinal bleeding and seemed to potentiate NSAID-associated bleeding[9], the authors suggested that this different presentation may result from higher proportion of alcohol consumption in male than female. Another possible hypothesis responsible for this finding was that different level of concern about their health between both sexes. Previous study reported that female patients made significantly more medical visits than male[10]. The authors suggested that males may tend to see a doctor in only serious situation like gastrointestinal bleeding, while females have more self-concern about their health problem. Although the initial clinical presentation was different between males and females, the percentage of advanced-stage adenocarcinoma at the first diagnosis was not significantly different in our findings.

Regarding locations of tumor, the presented data demonstrated that gastric cancer can developed in any locations. Surprisingly, in contrast with prior studies in most countries[11] including Thailand[5], the endoscopic findings showed that tumors predominately located in the proximal part (fundus and cardia) of the stomach. In most countries non-cardia gastric cancer presents more commonly than cardia gastric cancer with an average ratio of 2: 1[11]. However, some previous studies reported that the incidence of cardia gastric cancer in the western countries has substantially increased over time. The pathophysiological mechanism responsible for this major change is still inconclusive. The possible hypothesis is that prevalence of gastro-esophageal reflux disease has increased significantly over the past several decades. Although *H. pylori*-related cardia cancer has progressively declined since the mid-20th century in consonance with decreased prevalence of *H. pylori*, the incidence of reflux-related cardia cancer has gradually increased[12].

Many evidences suggested that environmental exposures played a vital role in development of gastric cancer. Even though there were small proportion of patients with *H. pylori* infection who developed gastritis-associated diseases including gastric cancer[13]. Several epidemiological studies supported *H. pylori* infection as a major contributing factor of gastric cancer. They demonstrated that concurrent or previous *H. pylori* infection was associated with an increased risk of gastric cancer with reference to uninfected people[3]. Determination of *H. pylori* status in gastric cancer patients might be problematic due to gastric mucosal change. Atrophy or metaplasia of gastric mucosa can lead to false-negative result and underestimation of *H. pylori* detection if only non-serologic methods such as routine histology and culture from biopsy specimen were used[14,15]. As patients in this present study were detected *H. pylori* by rapid urease test and/or urea breath test method, the positive result of investigation may be less than reality because of atrophic or metaplastic change[14-16]. Several studies suggested that serology method by evaluation of serum *H. pylori* antibody status was helpful diagnostic testing for bacterial infection especially in the case of gastric atrophy, intestinal metaplasia, dysplasia or gastric cancer[14,15]. Nonetheless, early *H. pylori* surveillance and eradication can bring considerable benefits to patients with a highly cost-effective method.

Similar to previous study in Thai patient[5], the majority of cases in the authors' study was stage IV and the most common pathologic type was adenocarcinoma.

HER2 is a transmembrane tyrosine-kinase receptor that regulates cell proliferation, differentiation, and survival[4]. Several literatures reported that positivity of HER2 in gastric cancer associated with poor prognosis, increased aggressiveness of disease and shorten survival[4,17], however, some other studies reported no significant correlation between HER2 status and prognostic outcome[18,19]. In addition to prognostic value, HER2 status determination in gastric cancer diagnosis was more taken into account because of its therapeutic benefit. The Trastuzumab for Gastric Cancer (ToGA) trial evaluated the use of trastuzumab, a monoclonal antibody against HER2, combined with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer. Results of the study demonstrated that trastuzumab in combination with chemotherapy was associated with extended median overall survival and could be considered as a new standard treatment option for advanced gastric cancer patients[20]. The authors' findings showed that most of Thai patients had HER2-negative gastric cancer. However, availability of HER2 testing was still limited in tertiary hospital or medical school in many developing countries including Thailand. Because a small number of HER2 testing was done, HER2 prevalence and association with gastric cancer status may be inconclusive from this presented study. Further study about relationship between HER2 and gastric cancer may help physician in assessment of prognosis and making a decision on selecting patients for appropriate treatment.

There were some limitations in the present study. Firstly, data of the research was retrospective reviewed from medical records with small sample size leading to some missing information and limited interpretation. Secondly, some investigations were still limited resources in Thailand such as tumor marker like HER2 testing and advanced testing of *H. pylori*. Thus, there may be some false negative or inadequate result.

Conclusion

Gastric cancer was usually diagnosed late. The most common presenting symptom in males was upper gastrointestinal bleeding, while females usually presented with abdominal pain. Almost half of patients who underwent *H. pylori* testing had positive result and majority of HER2 results was negative. There was no obvious association between severity of disease and *H. pylori* or HER2 in this presented study.

What is already known on this topic?

Most studies of gastric cancer reported about epidemiological data including incidence, patient characteristics, associated risk factors, prognosis and treatment. There were some studies conducted in both western and eastern countries including Thailand. The most recent study which was conducted on Thai patients reported status of cases diagnosed with gastric cancer from 1994 to 1998.

What this study adds?

This manuscript demonstrated current status and changes in some clinical characteristics of gastric cancer over the past decade. Additionally, the authors aimed to explore clinical significance of new investigational tools such as HER2 status.

Potential conflicts of interest

The authors declare no conflicts of interest.

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