·Clinical Research·

Trends in clinical and prognostic characteristics of gastric cardia adenocarcinoma

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[Abstract] Background and Objective: The incidence of adenocarcinoma of the gastric cardia has recently increased. This study compared the clinicopathology and prognosis of patients with gastric cardia adenocarcinoma in different periods between 1984 and 2003. **Methods:** A total of 589 patients with pathologically confirmed gastric cardia adenocarcinoma hospitalized at the Sun Yat-sen University Cancer Center between 1984 and 2003 were divided into 5-year groups. Retrospective analysis of clinical and prognostic characteristics between the different 5-year groups was conducted. **Results:** The number of hospitalized patients increased by 134.5%, with an annual increase of 4.6%. Median age was 60 years, with an increase of 5 years. Patients aged between 55 years and 64 years decreased, while patients aged ⩾ 65 years increased. The male-to-female ratio was 2.88:1, with no significant change. The rates of patients with the stage-I and -II disease changed insignificantly, while patients with stage-III disease increased, and patients with stage-IV disease decreased. The 5-year survival rate of all the patients was 28.5%, which increased from 20.9% between 1984 and 1993 to 35.5% between 1994 and 2003. **Conclusions:** During the past 20 years, associated with the upward-trending incidence of gastric cardia adenocarcinoma, the admission rate at our hospital of patients with the tumor increased. The median age of the patients also increased. The ratio of men to women had no significant change. The proportion of patients with late-stage disease decreased and prognosis has improved.

Key words: Gastric cardia, neoplasm, pathology, prognosis

Gastric cardia adenocarcinoma (GCA) is one of the most common malignant tumors in China. In recent years, researchers abroad have reported a significant increase in the incidence rate for GCA.[1-3] Although there is still no statistical data for the epidemic of GCA in China, some regional research has shown an annual increase in the rates of hospitalization and treatment for this cancer.[4] To understand the clinicopathologic and prognostic characteristics of GCA, we selected 589 patients with adenocarcinoma of the esophagogastric junction seen at the Sun Yat-sen University Cance Center between 1984 and 2003. Then, we conducted a retrospective study to analyze their clinicopathologic data and prognostic outcomes.

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Information and Methods

Patient selection

Selection standards included (1) patients with pathologic diagnoses of adenocarcinoma of the esophagogastric junction type II (AEG II) and categorized for staging after surgery and (2) patients with complete follow-up data, where the time and status of these patients were carefully noted (that is, alive, dead, or withdrawal).

Exclusion criteria included (1) clinical data that were not complete and statistical analysis based on these data was not possible and (2) patients that had other malignant tumors or had histories of malignant tumors.

General information

In a continuous 20-year period of hospitalization and treatment at the Sun Yat-sen University Cance Center between January 1, 1984 and December 31, 2003, 752 patients with GCA were admitted and 589 patients were qualified for selection. There were 437 men and 152 women, with a median age of 60 years. All patients were categorized into the appropriate staging

for GCA according to the standard criteria of the International Union Against Cancer (UICC).

Statistical analysis

SPSS13.0 software was used for statistical analysis. Quantitative data were tested by an analysis of variance and numeral data were analyzed by a Chi-square test. Survival rate was be analyzed by the Kaplan-Meier method, where the survival curve was plotted, before being further examined by a log-rank test for variance. $P < 0.05$ indicated statistical significance.

Follow-up

The time for follow-up began on the surgical date for GCA and these follow-ups continued through April 31, 2009. Letters, telephone calls, and visits by patients to the outpatient department were the follow-up approaches. The average follow-up time was (152.9 ± 3.8) months and the rate of successful follow-up was 90.9% , in which time 396 patients died of the disease.

Results

Comparison of hospitalization and treatment of GCA in 20 years

In four periods (1984–1988, 1989–1993, 1994–1998, and 1999–2003), the total number of available beds for admission did not change and numbers of patients with GCA over these four periods were 84, 172, 136, and 197, respectively. Between 1999 and 2003, the number of patients increased by 134.5% when compared to patients from 1984 to 1988, which yielded an annual average rate of increase of 4.6%.

Comparison of age of onset and sex

Patient age ranged from 27 years to 86 years, with a median age of 60 years. In 20 years, the median age continued to increase by 5 years, where the median age for each period was a linear increasing trend ($P < 0.05$). In each period, the variation of patients of different ages showed statistical significance ($P < 0.05$). Further analysis revealed that the variations for patients ⩽ 44 years and patients between 45 years and 54 years had no significance ($P > 0.05$). Patients aged between 55 years and 64 years decreased, while patients ⩾ 65 years increased. The ratio of men to women was 2.88 to 1, in which men comprised 74.2% (437/589) and women 25.8% (152/589). The sex of patients in different periods showed no significance ($P = 0.160$) (Table 1).

Table 1 Clinical characteristics of 589 patients with gastric cardia adenocarcinoma in different eras

Item	1984–1988 [patient No.(%)]	1989–1993 [patient No. (%)]	1994–1998 [patient No. (%)]	1999–2003 [patient No.(%)]	Total [patient No. (%)]	*P*
Total	84	172	136	197	589	
Sex						
Male	68	133	94	142	437	
female	16	39	42	55	152	0.160
Age (years)						
Median age	58	58	60	63	60	0.000
⩽ 44	5 (6.0)	16 (9.3)	10 (7.4)	12 (6.1)	43 (7.3)	0.644
45–54	21(25.0)	46(26.7)	33(24.3)	41(20.8)	141(23.9)	0.602
55–64	41(48.8)	72(41.9)	60(44.1)	60(30.5)	233(39.6)	0.010
⩾ 65	17(20.2)	38(22.1)	33(24.3)	84(42.6)	172(29.2)	0.000
Stage						
I	7 (8.3)	9 (5.2)	12 (8.8)	18 (9.1)	46 (7.8)	0.514
II	22(26.2)	43(25.0)	34(25.0)	59(29.9)	158(26.8)	0.678
III	17(20.2)	69(40.1)	63(46.3)	75(38.1)	224(38.0)	0.001
IV	38(45.2)	51(29.7)	27(19.9)	45(22.8)	161(27.3)	0.000
Survival rate (%)						
5-year	17.4	22.7	34.6	36.5	28.5	
10-year	8.7	16.8	23.1	–	–	0.000

Comparison of clinical staging

According to the Sixth Edition of the UICC standard criteria for clinical staging of GCA, 4 patients had stage-Ia disease, 42 patients had stage-Ib disease, 158 patients had stage-II disease, 190 patients had stage-IIIa disease, 34 patients had stage-IIIb disease, and 161 patients had stage-IV disease. Table 1 shows that staging for GCA was different for each time period. As time advanced, the variations in patients with GCA in stages I and II had no statistical significance ($P > 0.05$), while the percent of patients with stage-III disease increased. The percent of patients with GCA in stage IV significantly decreased ($P < 0.05$).

Comparison of survival rates

The 5- and 10-year survival rates for patients with GCA in different pathologic staging were compared and results demonstrated that the 5-year survival rate for all patients was 28.5%. The 5- and 10-year survival rates for patients with GCA in stage I were 61.2% and 43.0%, respectively, yielding an average survival of (120 ± 15) months. The rates for patients with GCA in

stage II were 54.6% and 33.9%, respectively, with an average survival of (95 ± 8) months. The rates for patients with GCA in stage III were 18.7% and 15.4%, respectively, with an average survival of (43 ± 4) months. The 5-year survival rate for patients with GCA in stage IV was 5.0%, with an average of (16 ± 2) months. The 5- and 10-year survival rates for patients with GCA in different periods were calculated and compared for analysis. Results showed that patients with GCA from 1994 to 2003 had significantly higher survival rates than patients in 1984 to 1993, where the 5-year survival rates were 35.5% and 20.9%, respectively ($P < 0.05$) (Table 1, Figure 1).

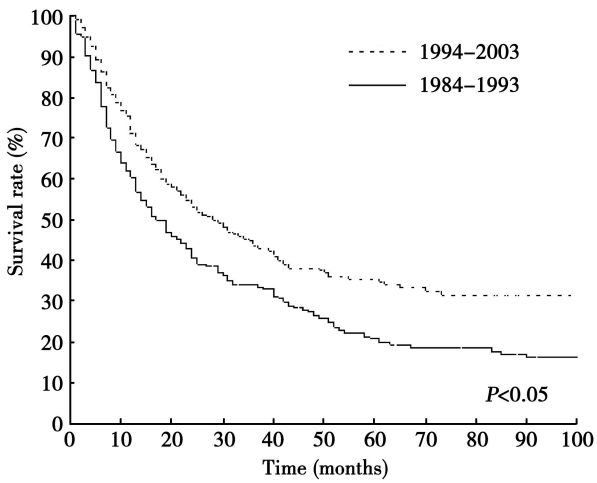

Figure 1 Survival analysis of patients with gastric cardia adenocarcinoma in different eras

Discussion

Currently, there is still no unifying standard in defining GCA. Clinically, malignant tumors, which primarily locate in the lower segment of the esophagus and at the proximal ends of the gastric cardia or below it, could also infiltrate the junction site between the stomach and the esophagus. Therefore, it is difficult to determine the original onset site of the tumor. Generally, we call any adenocarcinoma located at the junction site between stomach and esophagus GCA.[5]

Around the world, different countries have different concepts of and definitions for GCA.[6-8] Currently, the most accepted definition for GCA is the AEG classification proposed by Siewert *et al*.[9] in 1998. In 1998, the International Gastric Cancer Association (IGCA) and the International Society of Diseases of the Esophagus (ISDE), together, defined any tumor located within 5 cm above or below the anatomical esophagogastric junction (EGJ) line as adenocarcinoma of esophagogastric junction (AEG), also known as cancer of the cardia region. The cancer is classified into three types based on its anatomical location. Type I AEG is when the center of the tumor is located 1 cm above the EGJ line and is considered cancer at the distal end of the esophagus. It usually originates from a specific metaplastic region in the intestinal epithelium (also known as Barrett's esophagus) and it infiltrates downward to the EGJ. Type II AEG is when the center of the tumor is located 1 cm above and 2 cm below the EGJ line and is considered the true esophagogastric cancer. It originates from a metaplastic region in the intestinal epithelium at the anatomical EGJ. Type III AEG is when the center of the tumor is located at least 2 cm away from the EGJ line and is considered cancer at the proximal end of the stomach. It is usually referred to as adenocarcinoma of the stomach and it will infiltrate upward toward the cardia and the lower end of the esophagus.

GCA, as a malignant tumor, continues to show an increase in incidence in the population. In developed countries, the incidence rate for GCA is reported to have increased by 5 to 6 folds over the past few decades.[10,11] In United States and the United Kingdom, GCA accounted for about 50% of gastric cancer in men.[12,13] In developing countries, such as India, the incidence rate of GCA is also increasing.[14] China still lacks epidemiologic data on GCA. There were reports that in general hospitals in several provinces, including Gansu, the rate of patients with GCA increased to 37.1% in 2004 from 29.6% in 1993 ($P < 0.01$). It was also found that although the overall incidence rate for gastric carcinoma in China was decreasing (approximately 21.8/100 000),[15] the rate of confirmed gastric carcinoma at the proximal end and GCA increased gradually over the past years in Gansu Province, while the rate of gastric carcinoma at the distal end decreased.[4]

In this study, compared with the data in 1999–2003, in 1984–1988, the number of admitted and treated patients with GCA at the Sun Yat-sen University Cancer Center increased by 134.5%, yielding an average annual increase of 4.6%. Although the remission rate was different than the incidence rate, with exception to changes in this rate due to other factors, the data from this research matched the gradual increasing trend that we observed for the incidence rate of GCA around the world.

In this study, the median age of onset for these patients was 60 years, which was similar to other reports.[4,16,17] From 1999 to 2003, the median age increased by 5 years compared to patients from 1984 to 1988. The percent of patients aged 55 years to 64 years decreased, while the percent of patients of aged 65 year and older increased. This suggests that there were more elderly patients with GCA and there was an increasing pattern in this population. This shift in the age of onset for GCA could possibly be related to the aging of society and changes in the social environment. Reports from the Gansu Province also showed that the percent of patients with GCA at 50 years or above was 84.9%.[4]

Sex is also a risk factor for GCA and reports demonstrated that men were more prone to it.[16] Chinese researchers reported that the gastric cardia was the predilection site for gastric carcinoma in men, comprising 28.2%, which was 5.25 times the incidence in women.[4] The data from this study also showed that the ratio of men to women was 2.88 to 1, which was similar to other reports. However, the reason for the increase in the incidence rate of GCA due to sex differences remains unclear. With the exception to susceptibility due to genetic inheritance, it could possibly be related to other known risk factors, such as

smoking and drinking.[18]

Experimental data showed that as time advanced, the percent of patients with GCA in stages I and II were not altered, while the percent of patients with GCA in stage III increased and the percent of patients with GCA in stage IV decreased. The decrease in the number of patients with advanced-stage disease was because the diagnostic technique had improved and the general population had become more aware of health issues. However, because of the lack of specific clinical symptoms in the early stages of GCA, the course of the disease had actually entered the mid- or late-stage when symptoms, such as difficulty in swallowing, vomiting, nausea, and pain, emerged. Thus, there was no increase in the number of patients with early-stage disease.

Reports have declared poor prognostic outcomes for GCA, where the 5-year survival rate after surgery was 20.2%–35.3%. This study showed the 5-year survival rates for patients with GCA in stages I, II,III, and IV from 1984 to 2003 were 61.2%, 54.6%, 18.7%, and 5.0%, respectively. The 5-year survival rate for all patients with GCA was 28.5%, which was similar to other reports. As time advanced, the survival rate gradually increased. The 5-year survival rate for patients between 1999 and 2003 increased to 36.5%. The change in the survival rate was closely related to improvements in diagnostic techniques, improvements in therapeutic approaches, and an increase in public health awareness.

With gradual increases in the global incidence rates for GCA, epidemiologic study is warranted to further identify the disease progress. For populations with high risk and vulnerable individuals, gastroscopy should be recommended and great effort should be undertaken to increase public health awareness for GCA. This will allow us to improve early diagnosis and early treatment, hoping to significantly impact the treatment outcomes. Also, it should consider the increase in the number of elderly patients with GCA, to allot more resources and care for aging adults. Appropriate individualized therapy should be designed to achieve the best results.

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