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Clinicopathological characterisation of small (2 cm or less) proximal and distal gastric carcinomas in a Chinese population

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Summary

Clinicopathological characteristics of small gastric carcinoma have not been well defined in Chinese patients. The aim of this study was to investigate and compare small proximal (PGC, $n = 111$) with distal (DGC, $n = 202$) gastric carcinoma in 313 consecutive surgically resected small (≤ 2 cm) gastric carcinomas diagnosed with the WHO criteria. PGC patients were significantly older (average age 63 years versus 59 in DGCs) with a male/female ratio of 3:1. Most tumours were clustered along the lesser curvature (74% in PGCs and 65% in DGCs). Compared to DGCs, PGCs showed a protruded gross pattern significantly more frequently and were significantly better differentiated with a significantly wider histomorphological spectrum. Surprisingly, PGCs were composed of significantly fewer signet-ring cell carcinomas (1% versus 16% in DGCs) but were significantly more deeply invasive, compared to DGCs. Lymph node metastasis was detected in 23% overall, but was significantly less frequent in PGCs (16%) than in DGCs (26%) ($p < 0.05$). However, the difference in survival between the two groups was not statistically significant. Our results demonstrate that in Chinese patients, PGCs display distinct clinicopathological characteristics, compared to DGCs.

Key words: Cardia, Chinese, gastric cancer, *Helicobacter pylori*.

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INTRODUCTION

Gastric carcinoma is a heterogeneous disease. For instance, a rising incidence of proximal gastric carcinoma (PGC) has been reported almost worldwide, in contrast to a declining trend of distal gastric carcinoma (DGC).[1,2] Morphologically, PGCs display a wider variety of uncommon histological subtypes than the typical intestinal, diffuse, or mixed histology of DGCs.[3,4] Differences in molecular underpinning have also been reported. For example, HER2 and Sirt1 genes are more commonly expressed in PGCs than in DGCs.[4,5] Gene expression arrays have shown variations in signal transduction pathways between PGC and DGC.[6,7] Some authors provide evidence for two aetiologies for PGCs: some are akin to oesophageal adenocarcinoma (EAC) and related to gastroesophageal reflux disease, whereas others are similar to DGC and associated with *Helicobacter pylori* infection and atrophic gastritis.[8–11] Collectively, these observations favour PGC and DGC being different diseases.

Despite recent advances in our understanding of PGC, detailed clinicopathological studies of PGC in populations at high risk for gastric carcinoma remain rare. Many previous investigations include large, advanced neoplasms that obliterate the landmark of the gastroesophageal junction (GEJ).[3,12] This makes difficult a confident determination of the proximal gastric origin of a tumour. Complexity also stems from the controversial anatomical definition of the gastric cardia.[13–15] However, the exact anatomical distribution of PGCs is important to define, since recent GEJ cancer staging guidelines, which appear to be adequate for Western patients, have been shown to be flawed for East Asian populations.[16,17] Thus, the present study was aimed to systematically investigate PGCs and to compare their clinicopathological characteristics with DGCs in a homogenous Chinese patient population with high risk for gastric cancer but very low incidence of Barrett's oesophagus and EAC.[18] We specifically restricted our study to small PGCs measuring up to 2 cm in size to allow a better preservation of histological landmarks of the GEJ in order to eliminate any misclassification of gastric cancer as oesophageal in origin.

MATERIALS AND METHODS

Study group

All surgical pathology reports with a final diagnosis of gastric carcinoma from January 2004 through December 2011 were mined from the electronic pathology database of the Nanjing Drum Tower Hospital in China. Each report was reviewed for demographics, tumour gross and microscopic characteristics, and staging information. Inclusion criteria were: (1) surgically resected tumours with lymph node dissection; and (2) tumour size up to 2 cm in maximum dimension. Exclusion criteria included: (1) endoscopically resected tumours by mucosal resection or submucosal dissection without lymph node dissection; (2) tumour size larger than 2 cm; (3) no definitive invasion identified upon review of all histology slides; (4) tumours with the epicentre located in the distal oesophagus with a minor component of invasion into the proximal stomach; (5) tumour in the gastric stump from a patient with prior partial gastrectomy; (6)

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the absence of tumour tissue blocks for recuts; (7) neoadjuvant therapy; and (8) a distinct synchronous tumour detected within a minimal distance of 2 cm from the main tumour.

Patient medical records including radiology and endoscopy reports, laboratory study results, and surgical operative notes were reviewed. In 30% of the cases that were referred for surgery to the Nanjing Drum Tower Hospital but with detailed pre-operative radiology and endoscopy performed at outside institutions, the analysis was carried out principally on the local operative notes and resection specimen pathology findings. Patients were followed up for survival status through telephone or personal interview with the patient or family members. Results were verified with the government citizen death record. Patient consent for surgery and research was obtained in all cases before surgical resection was carried out. The Medical Ethics Committee of the Nanjing Drum Tower Hospital approved the study protocol.

Definition of carcinoma location, type, grade, and staging

All cases were divided into PGC and DGC groups, based on the location of tumour's epicentre. PGCs were defined as tumours with the epicentre located within 3 cm below the GEJ.[3,19] All other tumours distal to this 3 cm line were grouped as DGCs.

Gastrectomy specimens were routinely processed.[3,4] Partial gastrectomy for PGCs was carried out by an abdominal trans-hiatal approach with at least 2 cm of distal oesophagus resected. Tumour gross characteristics were obtained from pathology reports, including size, shape, surface, colour, consistency, the relationship to GEJ, resection margin, and the quality of adjacent gastric or oesophageal mucosa. Gross and endoscopic digital images were reviewed, if available. All tumours were macroscopically classified into five patterns, based on previously published classification:[20] (1) protruding with a broad base; (2) elevated with a rough surface; (3) flat without elevation or depression; (4) depressed with an eroded surface; and (5) excavated with an ulcerated centre and a defined border.

All tumours were classified as adenocarcinoma, adenosquamous and mucinous carcinomas, carcinoma with lymphoid stroma, or poorly cohesive (including signet-ring cell) carcinomas, using the WHO scheme.[20] A well-differentiated tumour exhibited well-formed papillae or tubules in over 95% of the tumour, in contrast to a poorly differentiated carcinoma with irregular or indiscernible glands in less than 50% of the tumour. In cases with morphological features suspicious for neuroendocrine carcinoma, adenocarcinoma with pancreatic differentiation, and carcinoma with lymphoid stroma,[3] appropriate immunohistochemical (i.e., synaptophysin, chromogranin A, CD56, α1-chymotrypsin) and *in situ* hybridisation evaluations for Epstein–Barr virus (EBV) were performed with standard protocols.

Lymphovascular and perineural invasion and the status of resection margins were recorded. In cases with no carcinoma identified in routine sampling, the entire gastric mucosa was submitted for histological examination.

All tumours were staged by the 7th edition of the American Joint Committee on Cancer (AJCC) staging guidelines.[21]

Evaluation of adjacent uninvolved gastric mucosa

The presence or absence of chronic active gastritis, metaplasia (i.e., intestinal or pancreatic), *Helicobacter pylori* infection (based on haematoxylin-eosin and Giemsa stains), and atrophy (defined as either a reduced number of glands or intestinal metaplasia) were recorded, based on the WHO definitions.[20]

Immunohistochemistry

Using conventional methods,[3–5,22] immunohistochemistry was performed on selected cases. The antibodies used were purchased from government-approved vendors. Appropriate positive and negative controls were included in each run.[3–5,22] Two experienced pathologists, blinded to the patient's clinical information, reviewed each immunostain independently. The discrepancy between readers was minimal, when present, and resolved by consensus.

In situ hybridisation for EBV-encoded small ribonucleic acid-1

EBV *in situ* hybridisation, as described previously with minimal modification,[23] was carried out on tumour sections that were sequentially deparaffinised, rehydrated through graded ethanol solutions in a decreasing order down to water, then predigested with 0.4% peptidase, and hybridised overnight at 37°C with digoxigenin-labelled probes, based on the manufacturer's instructions (Zhongshan Jingqiao, China). The positive control consisted of Burkitt's lymphoma, and a normal lymph node served as the negative control. Both controls were run in each batch to ensure validity.

Statistical analysis

Patient age, gender, *Helicobacter pylori* status, tumour location, gross pattern, size, grade, type, stage, lymphovascular and perineural invasion, adjacent uninvolved mucosa, and resection margin status were analysed and compared between PGC and DGC groups with the Chi-square or Fisher's exact test, when appropriate. Survival rates were estimated by the Kaplan–Meier method with a log rank test. The Cox regression analysis was used to identify risk factors for overall survival. All analyses were carried out with the Statistical Package for Social Sciences (Version 13; SPSS, USA). p values <0.05 were defined as statistically significant.

RESULTS

Within the 8-year study period, 313 consecutive patients met the inclusion criteria. The patients were divided into PGC ($n = 111$, 35%) and DGC ($n = 202$, 65%) groups (Table 1). The average number of tumour-bearing histology sections reviewed was 3.5 (range 1–13) per case.

Demographics

Male gender was predominant in both PGC and DGC groups, but the male/female patient ratio was significantly higher in PGCs than in DGCs (3.1 versus 1.7, $p < 0.05$). The average age of patients was also significantly older in PGCs (63 years) than in DGCs (59 years, $p < 0.05$). There were no patients younger than the age of 40 in the PGC group.

Tumour distribution and macroscopic characteristics

Overall, the majority (68%) of tumours arose along the lesser curvature, mainly in two areas, the cardia and antrum (Table 1 and Fig. 1). The remaining tumours were scattered in the corpus, pylorus, and the greater curvature.

Macroscopically (Table 1), excavated tumours were most frequent (61%) overall, but significantly less so in PGCs ($p < 0.01$). Protruding tumours (Fig. 2) were generally infrequent (7%), but more common in the PGC group than in the DGC ($p < 0.0001$). Elevated, flat, and depressed patterns were less common in PGCs than in DGCs.

Table 1 Comparison of tumour gross characteristics

Gross feature	PGC (%) (n=111)	DGC (%) (n=202)	p
Size (cm)			
Average ± SD	1.6 ± 0.47	1.5 ± 0.5	NS
Range	0.3–2.0	0.3–2.0	
Epicentre location			
Gastroesophageal junction	10 (9)	–	
Fundus	5 (5)	–	
Lesser curvature	82 (74)	132 (65)	NS
Greater curvature	6 (5)	16 (8)	NS
Anterior/posterior wall	8 (7)	7 (4)	NS
Antrum/anterior	–	18 (9)	
Incisura	–	14 (7)	
Corpus	–	6 (3)	
Pylorus	–	9 (4)	
Gross feature			
Protruded	16 (15)	6 (3)	0.0001
Elevated	14 (13)	18 (9)	NS
Flat	6 (5)	12 (6)	NS
Depressed	18 (16)	27 (13)	NS
Excavated	57 (51)	139 (69)	0.005

DGC, distal gastric carcinoma; NS, not significant; PGC, proximal gastric carcinoma; SD, standard deviation.