Pathology (October 2015) **47(6)**, pp. 526–532

OPEN

ANATOMICAL PATHOLOGY

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*.

Received 1 January, revised 10 April, accepted 20 April 2015

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)

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.1097/PAT.0000000000000276

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.

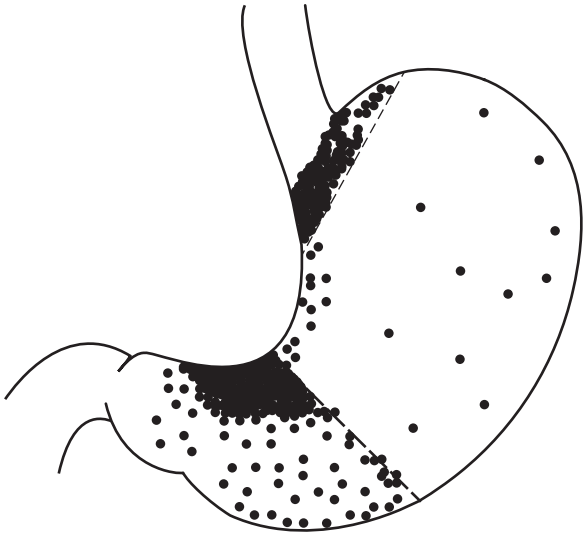

Fig. 1 Distribution of small (≤2 cm) gastric carcinomas. Note the two concentrated regions of tumours along the lesser curvature of the cardia and the antrum separated with broken lines from the gastric corpus.

Histopathology of small proximal gastric carcinomas

Compared to DGCs (Table 2), PGCs were significantly better differentiated ($p < 0.001$) and exhibited a wider histopathological spectrum. While tubular adenocarcinoma was most common, pure and mixed mucinous carcinomas were predominant among PGCs. Mixed squamous (Fig. 3A) and neuroendocrine carcinomas were found only in PGCs. Papillary adenocarcinoma (Fig. 3B) also occurred significantly more frequently in PGCs (30%) than in DGCs (5%) ($p < 0.0001$). A small proportion (9%) of PGCs arose in mucous glands at the GEJ and showed an expansile growth pattern with anastomosing glandular architecture without evidence of columnar-lined oesophagus with intestinal metaplasia (Fig. 3C). Micropapillary (Fig. 3D), pure mucinous, pure neuroendocrine (Fig. 3E) carcinomas, and carcinoma with lymphoid stroma (confirmed with the positive *in situ* hybridisation test for EBV, Fig. 3F) were also more common in PGCs than in DGCs, but the differences were not statistically significant. In contrast, pure and mixed signet-ring cell carcinomas were significantly less common in PGCs than in DGCs ($p < 0.001$). Poorly cohesive carcinoma (excluding signet-ring cell carcinoma) was also less common in PGCs than in DGCs (Table 2). There were no significant differences between the two groups in tumour size, lymphovascular and perineural invasion, and resection margin status.

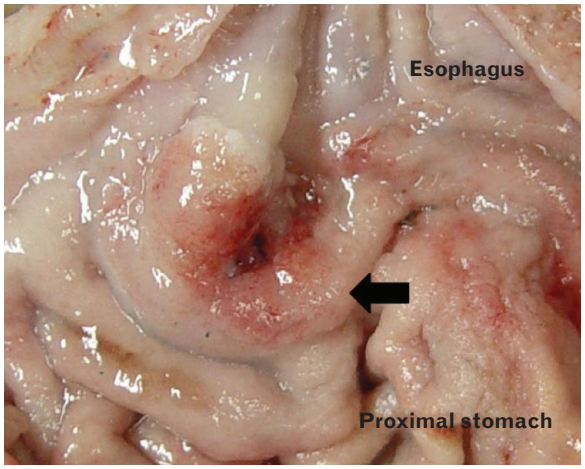

Fig. 2 Representative gross image of a proximal gastric carcinoma located below the gastroesophageal junction and showing a broad-based protruding tumour with a rough surface (arrow).

Table 2 Comparison of histopathology

Microscopic characteristics	PGC (%) ($n = 111$)	DGC (%) ($n = 202$)	p
Tumour differentiation			
Well	22 (20)	17 (8.5)	0.0002
Moderately	45 (41)	59 (29)	
Poorly	44 (39)	126 (63)	
Histology type			0.0000
Adenocarcinoma			
Tubular	50 (45)	106 (52)	
Papillary	34 (30)	10 (5)	
Mixed signet-ring cell	5 (5)	32 (16)	
Mixed mucinous	5 (5)	2 (1)	
Mixed squamous cell	2 (2)	0	
Mixed neuroendocrine	2 (2)	0	
Poorly cohesive adenocarcinoma*	3 (3)	18 (9)	
Signet-ring cell carcinoma	1 (1)	32 (16)	
Mucinous carcinoma	2 (2)	0	
Carcinoma with lymphoid stroma	2 (2)	1 (0.5)	
Neuroendocrine carcinoma	5 (2)	3 (1.5)	
Perineural invasion	23 (21)	44 (21)	NS
Lymphovascular invasion	22 (20)	45 (22)	NS
Positive surgical resection margin	3 (3)	3 (1.5)	NS
Adjacent gastric mucosa			
Chronic active inflammation	107 (96)	199 (98.5)	NS
Atrophic mucosa/intestinal metaplasia	97 (87)	176 (87)	NS
Helicobacter pylori	59 (53)	150 (74.25)	0.0005
Pancreatic metaplasia	27 (24)	0	0

DGC, distal gastric carcinoma; NS, not significant; PGC, proximal gastric carcinoma; SD, standard deviation.
* Excluding signet-ring cell carcinoma.

Histopathology of adjacent gastric mucosa

The frequency of chronic active gastritis, intestinal metaplasia and atrophy was similar in both groups (Table 2). Pancreatic metaplasia was found only in PGCs. The frequency of *Helicobacter pylori* infection was significantly lower in PGCs than in DGCs ($p < 0.001$).

Pathological staging

Partial gastrectomy (92%, 288/313) with D1 nodal dissection (88%, 277/313) was carried out in the vast majority of cases with an R0 resection rate of 91.7% (287/313) for the cohort. The overall difference in the pT stage between PGC and DGC groups was statistically significant (Table 3, $p < 0.05$). The proportion of pT1 tumours was smaller in PGCs than in DGCs, but the frequency of advanced tumours in pT3 and pT4 was higher in PGCs than in DGCs (Table 3). The average number of lymph nodes retrieved per case was 18.8 (17.1 in PGC and 19.7 in DGC). Lymph node metastasis was found in 23% of all cases, but the frequency was significantly lower in PGCs (16%) than in DGCs (26%) ($p<0.05$). The only case with distant metastasis was in the DGC group, in which a poorly differentiated, mixed carcinoma with both signet-ring cell and pancreatic acinar-like differentiations[3,22] metastasised to the ovary in a 29-year-old woman. In the summary stage, the number of patients staged as pIII was smaller in the PGC group than in the DGC. There was no pIV case in the PGC group.

Patient survival

Sixty-five (21%) patients, 28 (25%) in the PGC group and 37 (17%) in the DGC, were lost to follow-up and excluded from

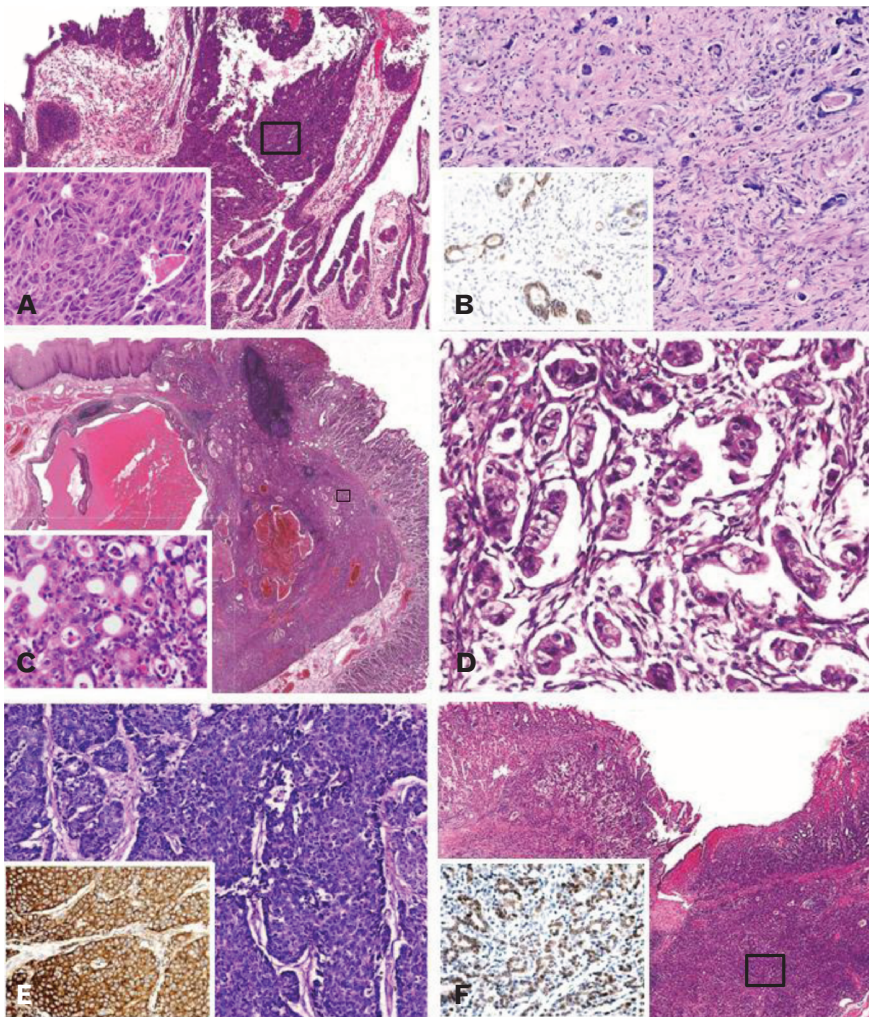

Fig. 3 Histological types of proximal gastric carcinoma. (A) Adenosquamous carcinoma showing both glandular and squamous (square area is enlarged in the inset) components. (B) Pancreatic acinar-like adenocarcinoma features infiltrative small neoplastic acini with dense purplish, granular cytoplasm and immunoreactivity to α1-chymotrypsin (inset: immunostain). (C) Proximal gastric carcinoma crossing the gastroesophageal junction demonstrates anastomosing (rectangular area is enlarged in the inset), expansile growth patterns. Note the dilated oesophageal gland duct on the left. (D) Micropapillary adenocarcinoma. (E) Neuroendocrine carcinoma. Inset: the immunoreactivity to synaptophysin is demonstrated. (F) Carcinoma with lymphoid stroma shows an expansile growth pattern and a sharply demarcated pushing border at the invasion front. Inset: presence of Epstein–Barr virus in the nuclei (*in situ* hybridisation).

the survival analysis. At the last interview, 24 (10%) patients had died, eight (7%) in the PGC group and 16 (8%) in the DGC. Although the mean survival in PGCs [84.7 months, 95% confidence interval (CI) 79.3–90.2] was shorter than that in DGCs (94.4 months, 95% CI 89.6–99.1), the difference between the two groups was not statistically significant ($p = 0.6$) (Fig. 4). There was no significant difference in survival between the two groups in stage-by-stage or year-by-year comparisons. Multivariate analysis identified age $\geq$61 years [odds ratio (OR) 2.6; $p < 0.05$], pT3 (OR 13.3; $p < 0.001$), and pT4 (OR 3.4; $p < 0.05$) tumours as significant independent risk factors for worse overall survival.

DISCUSSION

In line with previous studies,[3,6,24] our data show a predominant distribution pattern of small gastric carcinoma along the lesser curvature for both PGCs and DGCs. However, compared to DGCs, PGCs demonstrate the following distinct clinicopathological characteristics: (1) elderly male predominance; (2) more protruded and fewer excavated macroscopic growth patterns; (3) better histological differentiation and a wider morphological spectrum but fewer signet-ring cell carcinomas; (4) deeper invasion but fewer lymph node metastases; and (5) lower frequency of *Helicobacter pylori* infection and exclusive association with pancreatic metaplasia. All together, we believe that these data, although yet insufficient to support classifying PGC as a unique subtype of gastric cancer, underscore the difference between two topographically distinct gastric carcinomas.

In recent years, some investigators have proposed that PGCs be considered as part of the distal EAC spectrum,[12] based on the assumption that PGC may originate from undetected short-segment Barrett's oesophagus. The results from the present cohort and a previous study in the same Chinese patient population have shown otherwise.[3,18] In Chinese patients, distal oesophageal Barrett's oesophagus and EAC are rare,[18] but PGC is common and histologically heterogeneous.[3] In contrast, almost all distal EACs are pure adenocarcinomas of the intestinal phenotype (Lauren classification).[3,22] Furthermore, the AJCC pathological staging rules for GEJ cancer have been found deficient when applied to PGCs with oesophageal invasion in both East Asian[16,17] and European[25] populations. The discrepancy may result, at least partially, from misclassification

Table 3 Pathological (pTMN) staging

Pathological staging (pTNM)	Proximal (PGC, %)	Distal (DGC, %)	*p* (PGC vs DGC)
Total cases	111	202	
pT			0.0343
1	61 (55)	129 (64)	
1A	30 (27)	82 (40.5)	
1B	31 (28)	47 (23)	
2	26 (23)	38 (19)	
3	11 (10)	14 (7)	
4	13 (12)	21 (10)	
4A	6 (6)	3 (1.5)	
4B	7 (6.5)	18 (9)	
pN			0.048
0	93 (84)	149 (74)	
1	10 (9)	26 (13)	
2	6 (6)	15 (7.5)	
3a	2 (2)	12 (6)	
pM			NS
0	111 (100)	201 (100)	
1	0	1 (0.5)	
Summary stage			NS
I	84 (76)	140 (70)	
IA	56 (50)	109 (54)	
IB	28 (25)	31 (15)	
II	16 (14)	35 (17)	
IIA	10 (9)	27 (13.5)	
IIB	6 (6)	8 (4.5)	
III	11 (10)	26 (13)	
IIIA	1 (1)	6 (3)	
IIIB	6 (6)	13 (6.5)	
IIIC	4 (4)	7 (4)	
IV	0	1 (0.5)	

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

of large PGCs as distal EACs in previous studies.[12,26] Notably, European investigators have described such misclassification in a substantial number of cases, leading to a falsely increased incidence of EACs.[27]

At present, neither the AJCC nor the Siewert classification[28] reflect the cases examined in the Chinese population that we studied, in which almost all small PGCs have an epicentre much closer to the GEJ (<5 cm). As we have shown previously in Chinese patients, most Siewert's type II tumours (1 cm above and 2 cm below the GEJ) are likely to represent proximal gastric, but not distal oesophageal, tumours.[3] In addition, several Asian investigators have shown that Siewert's type III tumours (2–5 cm below the GEJ) present similar clinicopathological characteristics to DGCs.[29–32] Consequently, given the discrepancies and overlapping between these landmarks (developed primarily with the data from Caucasian patients) and the results obtained from Chinese patients, we chose to use tumour epicentre at 3 cm below the GEJ as a new landmark for PGC. Compared to DGCs, PGCs more often exhibit a macroscopically protruding pattern.[3] PGCs are also in general better differentiated and poorly cohesive carcinomas are unusual.[24] However, PGCs are more deeply invasive, a characteristic reported as an independent predictor of worse survival in several Japanese series.[24,33] Finally, pancreatic metaplasia was frequently detected adjacent to PGCs, a finding not described in association with distal EAC.[3,12]

Perhaps one of the most striking yet unexpected findings is a high overall lymph node metastasis rate of 23%, which is much higher than that reported in Japanese series evaluating early small carcinomas (≤2 cm in size) with poor prognostic indicators (ulcerative gross appearance and undifferentiated carcinoma histology).[34,35] In general, the prognosis of PGCs is reported to be worse than that of DGCs.[4,36–38] This is directly related to the more advanced pT stage, as previously described in Korean and Chinese patients.[37,38] Furthermore, in this cohort, advanced PGCs cases are rare (10% as pIII and none as pIV), but patients show shorter survival, compared to DGCs, although the difference in survival is not statistically significant. This observation, in our opinion, suggests the need for a large-scale survival study of PGC patients in order to better evaluate their prognosis and predisposing factors.[16,17,25]

Given the similar frequency of chronic active gastritis with intestinal metaplasia and atrophy in the mucosa surrounding both PGCs and DGCs, *Helicobacter pylori* infection remains the primary risk factor for gastric carcinomas in the Chinese population. However, since the actual incidence of *Helicobacter pylori* infection in PGCs is smaller, other risk factors may play important roles in the development of PGCs. Those risk

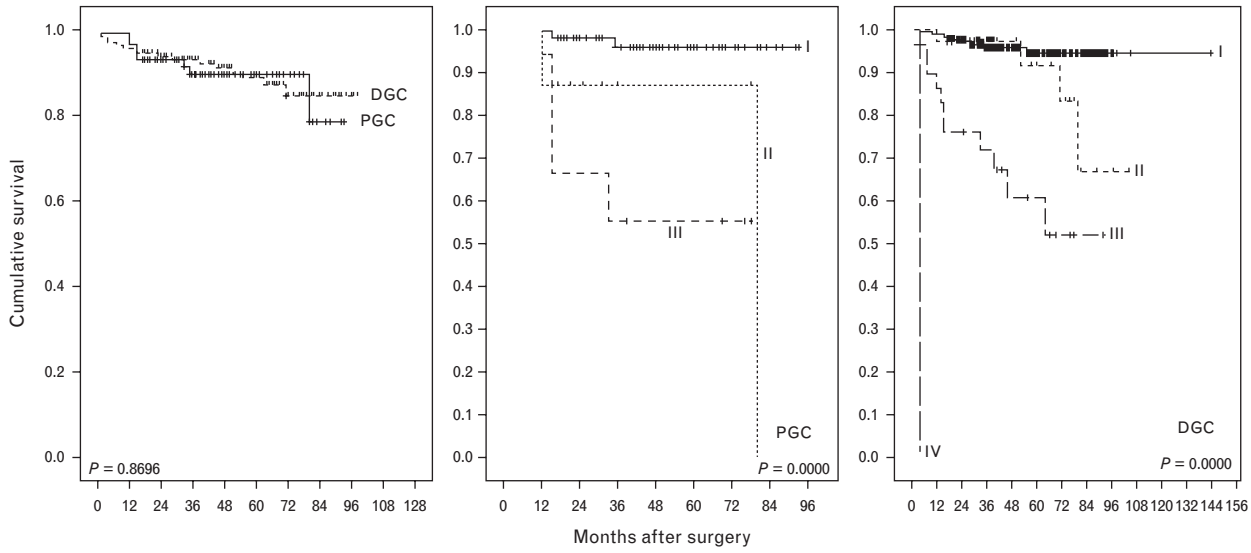

Fig. 4 Kaplan–Meier survival curves of patients with PGC or DGC tumours and staged as gastric carcinoma (AJCC 7). (A) There was no statistically significant difference between the PGC and DGC groups in overall survival outcomes. (B) Patients with PGCs were stratified according to different pathological stages; the difference in survival stratification was statistically significant. (C) Patients with DGC demonstrated an excellent stage-by-stage, statistically significant survival stratification difference ($p < 0.0001$).

factors may include tobacco abuse (epidemic in China) and obesity. Of note, two recent meta-analyses emphasise the relationship between increased body mass index and the risk of gastric cancer development, especially in the proximal stomach.[39,40]

Finally, using comparative genomic hybridisation, Japanese researchers have described statistically significant chromosomal gains and losses in 35 PGCs, compared to 67 DGCs.[41] In PGCs, the most common deletion is on chromosome 18q, where the tumour suppressor *smad* gene (a key regulator of the transforming growth factor-β signalling pathway) is located.[42] Recently, Canadian researchers have reported, in an abstract form, the presence of mutational differences between gastric cardia (PGC) and non-cardia (DGC) carcinomas.[7] Their findings are confirmed by the most recent data on comprehensive molecular characterisation of gastric carcinoma,[43] supporting the concept of pathobiological diversity between PGCs and DGCs.[7]

The major limitation of this retrospective study includes inherent deficiency in data uniformity, such as collection of tumour gross images, standardisation of endoscopic investigation with biopsies, and completion of survival investigation. A further limitation is the lack of results on adjuvant therapy, which could confound the survival data. Although such variables are difficult to control, the main findings of the study are unlikely to be adversely affected, because of the large sample size, strict exclusion criteria, and detailed histopathological investigations.

In summary, based on the evidence acquired from present and previous studies,[3,6,7,17,25] PGC can be characterised as an elderly male predominant, heterogeneous gastric carcinoma, frequently presenting with better differentiation, deeper penetration, and fewer nodal metastases, in comparison to DGC. Altogether, these results detail striking clinicopathological differences between PGCs and DGCs in the Chinese population. However, the data are yet insufficient to support classifying PGC as a unique subtype of gastric cancer.

Acknowledgements: The major results of this study were published in an abstract form in Gastroenterology 2012; 142 (5, *Suppl* 1): S627.

Conflicts of interest and sources of funding: This research project was financed partially by grants from the Science and Technology Development Project of the Nanjing City (ZKX05013, ZKX07011) in China, and a special grant from the Nanjing Drum Tower Hospital, Nanjing, China. JSG is supported by the Department of Veterans Affairs Office of Research and Development through a Career Development Award-2. The authors state that there are no conflicts of interest to disclose.

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