



CT findings in diagnosis of gastric bare area invasion: potential prognostic factors for proximal gastric carcinoma

Rui-Jia Sun¹ · Lei Tang¹ · Xiao-Ting Li¹ · Zi-Yu Li² · Ying-Shi Sun¹

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Abstract

Purpose To investigate the correlation between the preoperative CT findings in diagnosis of gastric bare area (GBA) invasion and the 3-year-overall survival (OS) of patients with proximal gastric carcinoma (PGC).

Methods 108 consecutive patients with PGC confirmed by biopsy underwent MDCT scan prior to gastrectomy were enrolled retrospectively from Dec 2009 to Dec 2014. GBA invasion in PGC were evaluated by measuring the direct CT signs including transmural involvement and lymph nodes in the GBA. The indirect signs were also evaluated including the infiltration of the diaphragm, gastrophrenic ligament and perigastric fat. Kaplan–Meier estimates with log-rank test and Cox proportional hazard model were used for analysis.

Results The two raters achieved excellent agreement. Univariate Kaplan–Meier estimates indicated that postoperative chemotherapy ($p=0.003$), transmural involvement ($p<0.001$), lymph nodes in the GBA ($p=0.015$) and cT staging ($p=0.002$) were associated with OS. Cox proportional hazard model indicated that the transmural involvement (HR = 8.194, 95% CI 2.15–31.266), diaphragm involvement (HR = 0.21, 95% CI 0.042–0.986), perigastric fat infiltration (HR = 0.125, 95% CI 0.018–0.885; HR = 0.02, 95% CI 0.001–0.264), and cT staging were independent prognostic factors for OS.

Conclusion CT findings of GBA invasion in patients with PGC, not only the transmural involvement but also the indirect signs are independent prognostic factors potentially, which should be given more emphasis in future clinical practice.

Keywords Gastric cancer · Anatomy · CT · Prognosis

Abbreviations

PGC	Proximal gastric carcinoma
GBA	Gastric bare area
MDCT	Multidetector computed tomography
cT	Clinical T stage
pT	Pathological T stages
LN	Lymph nodes

Introduction

Gastric cancer, a common malignancy with a poor prognosis, is listed as the second leading cause of cancer mortality worldwide [1]. Tumors of the esophagogastric junction are among the most frequent and lethal cancers. In addition, their incidence is increasing. Patients often do not present until late in the disease when the tumor is sufficiently large to cause obstruction or invasion of the adjacent structures, and thereby becomes symptomatic [2]. Contrast-enhanced multidetector computed tomography (MDCT) allows relatively noninvasive assessment of the gastrointestinal wall and various tumors [3]. MDCT techniques such as three-dimensional (3D) CT gastrography had also been used in diagnosis of gastric cancers [4–6].

Tumors originating in the cardia or the gastro-esophageal junction were usually addressed as proximal gastric tumors (PGC) [7]. Regarding the surgical treatment, no difference exists between PGC of anterior wall and those of posterior wall. Nevertheless, cancers of the posterior wall of proximal stomach are more difficult to cure than that of the anterior

✉ Ying-Shi Sun
sys27@163.com

¹ From Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Radiology, Peking University Cancer Hospital and Institute, No. 52 Fu Cheng Road, Hai Dian District, Beijing 100142, China

² From Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Surgery, Peking University Cancer Hospital and Institute, No. 52 Fu Cheng Road, Hai Dian District, Beijing 100142, China

wall [8]. The cause must consist of an anatomical characteristic, the fact that posterior wall of the fundus and subcardial portion (we call it gastric bare area, GBA) is not covered by the visceral peritoneum [8, 9], increasing the likelihood that these tumors will be diagnosed at a more advanced stage, may also be associated with unfavorable prognosis on proximal tumors.

To our knowledge, GBA space resembles an inverted triangle. The upper aspect of GBA is gastrophrenic ligament. Right side of GBA is marginated by the peritoneal reflection of upper recess of lesser sac and left side is defined by the peritoneal reflection between stomach and diaphragm, which was also called right and left gastrophrenic ligament, respectively [10].

The overall survival among patients with stomach cancer has remained stable at a low level for several decades. PGC is a distinct clinical entity compared with tumors located in other parts of the stomach with an increasing incidence and a poor prognosis. In previous studies, univariate analysis of Cox proportional hazards regression model revealed that the differentiation of gastric carcinoma, depth of invasion, number of positive lymph nodes, TNM stage, and external vascular invasion were relevant to prognosis [7, 8, 11]. To date, a curative therapy for gastric cancer mainly relies on the complete resection of the tumor; thus, early diagnosis and accurate evaluation are important for decision making regarding treatment and for the prognosis.

CT has been ascertained to have potential in the evaluation of tumor location, stage of the disease, and monitoring of therapy, but its value in the preoperative evaluation has not been completely established, especially to PGC with GBA invasion [12, 13]. The purpose of our study was to investigate the correlation between the preoperative CT findings in diagnosis of GBA invasion and the 3-year-overall survival (OS) of patients with PGC.

Methods

Patients

This retrospective study was approved by the institutional review board of our institute, and the requirement of informed consent was waived.

129 consecutive patients with PGC underwent MDCT scan prior to gastrectomy were enrolled retrospectively from Dec 2009 to Dec 2014. The inclusion criteria were as follows: (a) pathologically proven PGC; (b) complete CT images, including axial, coronal, and sagittal CT sections; (c) no chemotherapy or radiotherapy before surgery and (d) tumor resection performed within 2 weeks after the CT scan. The interval between MDCT examination and surgery was 1 day to 2 weeks (mean 6.7 days).

Patients were excluded if: (a) CT-detected metastasis or lymph nodes beyond GBA ($n=9$); (b) they died due to surgical complications ($n=4$); (c) they had other malignancy or gastric multiple primary carcinoma ($n=5$); (d) insufficient gastric distention ($n=3$).

In total, 108 patients who had undergone were enrolled in the study. The CT findings, pathological records, and clinical data for patients were retrospectively reviewed.

CT protocol

Multi-detector row was performed using a 64-detector row CT scanner (LightSpeed 64; GE Healthcare, Milwaukee, Wis). Each patient had been fasting for more than 6 h prior to the CT examination. To reduce gastric motility and enable gastric distention, the patients were given an intramuscular injection of 10 mg Anisodamine 10–15 min before the examination and received 8 g gas-producing crystals orally with 10 mL of water orally shortly before CT scanning. Upper abdominal unenhanced CT scans from the diaphragmatic domes to 2 cm below the lower margin of the air-distended gastric body were acquired. Subsequently, a total of 100 ml of non-ionic contrast medium (Ultravist; Schering, Berlin, Germany) was administered intravenously through an 18-gage angiographic catheter inserted into an antecubital vein at 3 mL/s by using an automatic injector. Contrast-enhanced CT scans were performed in the arterial phase (start delay, 30 s), in the portal venous phase (70 s). Unenhanced scan was also required for all patients. The CT parameters used were as follows: collimation of 0.625 mm, gantry rotation time of 0.5 s, tube voltage of 120–140 kVp, tube current–time product of 300–350 mAs, and table feed per rotation of 15 mm. Using these raw data sets, both the arterial and portal venous phase axial CT images were reconstructed with a 5-mm section thickness and a 5-mm reconstruction interval for clinical interpretation. To further analyze the status of serosa invasion, multiplanar reconstruction (MPR) images were done with section thickness of 0.625-mm.

Image analysis

Two abdominal radiologists (with 5 and 8 years of experience in abdominal CT, respectively) performed the image analysis. They were blinded to the clinical and survival data of patients. CT images were evaluated independently at the workstation by using transverse CT (5 mm) and MPR images (0.625 mm or greater) with soft-tissue window settings. Differences in assessment were evaluated by kappa coefficient analysis.

Wu et al [10] concluded the positive CT findings for GBA invasion. We classified them into direct signs and indirect signs. The direct signs including transmural involvement

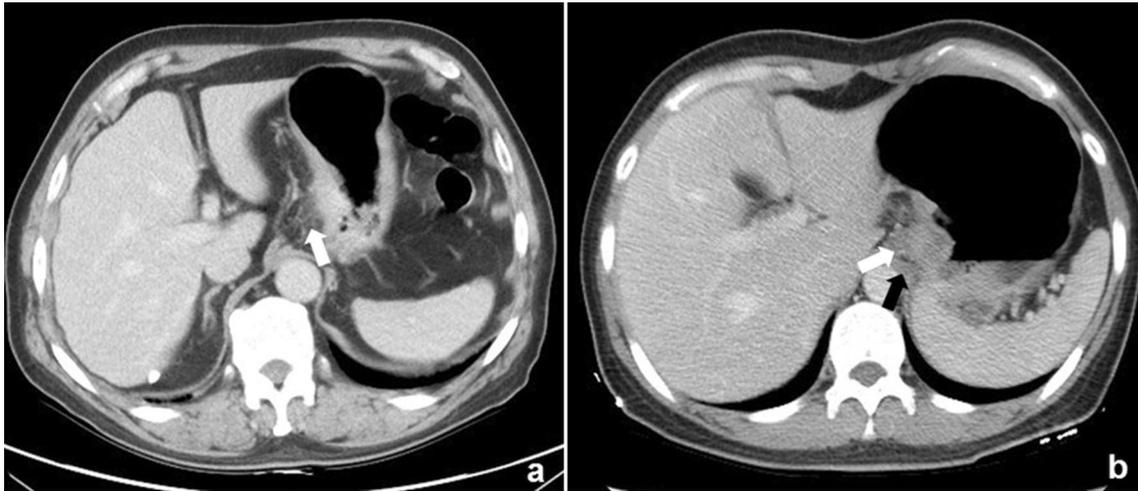


Fig. 1 **a** Proximal gastric cancer (pT4) in a 64-year-old woman. Axial MDCT shows an irregular tumor contour with small linear strands of soft tissue extending into the fat plane, which indicates transmural PGC with a blurring fat plane. **b** Proximal gastric cancer (pT4) in a

58-year-old man. Axial MDCT shows a transmural PGC with obliteration of the fat plane (white arrow) between the gastric wall and the left diaphragm and additional invasion of the later (black arrow)

and lymph nodes in the GBA (Figs. 1, 2). Arterial phase and portal venous phase were both used for image analysis. The following features were evaluated: MDCT depiction of tumors in relation to the GBA and the peritoneal reflection; the presence of tumor extra luminal extension; numbers of swollen lymph nodes (short axis > 5 mm) in the GBA or along the subphrenic retroperitoneal space.

The presence of the diaphragm and gastrophrenic ligament invasion, as well as the infiltration of perigastric fat, which were considered to be the indirect signs, were also evaluated. Diaphragmatic invasion is suggested when the

low-attenuation band of fat between the tumor and the diaphragm is absent, or when blurring and wide reticular strands surrounding the outer border of the diaphragm were identified (Fig. 1b). A fat stranding involving more than one-third of the tumor borders was defined as involvement or penetration of the perigastric fat. However, It is indicated that there is no invasion of the GBA when axial CT shows a smooth out layer of tumor and a clear perigastric fat plane (Fig. 3). The degree of fat infiltration was recorded as clear, blurring (Fig. 1a) and obliteration (Fig. 1b).

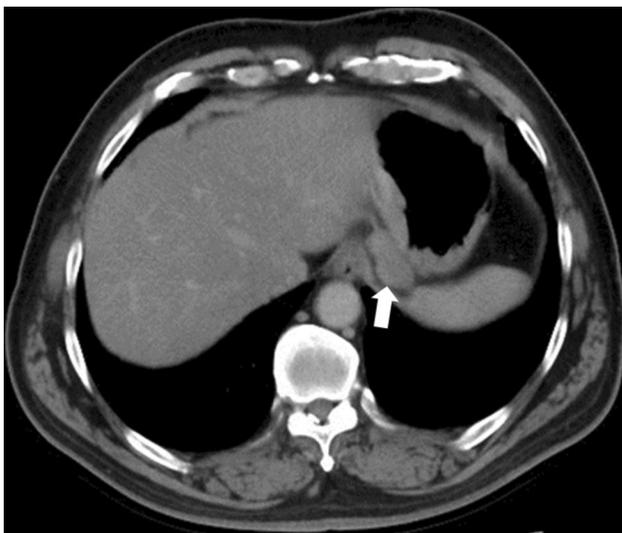


Fig. 2 Proximal gastric cancer (pT4) in a 58-year-old man. Axial MDCT image shows a 35×17 mm hypoattenuating lymph node (arrow) in GBA

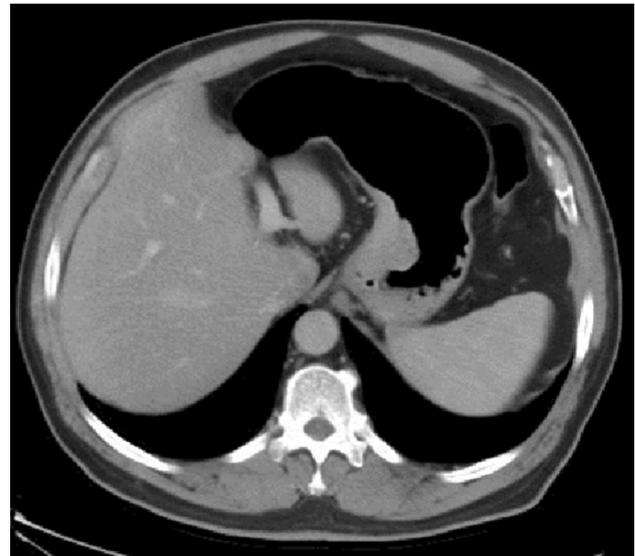


Fig. 3 Proximal gastric cancer (pT3) in a 63-year-old man. Axial CT shows a sharp tumor contour and a clear stomach fat plane

Table 1 Univariate analysis of prognostic factors according to OS

Prognostic factor	Number of patients (<i>n</i> = 108)	Rate	95% CI	<i>P</i> value
Age				0.570
≤ 62	55	0.711	0.588–1.946	
> 62	53	0.695	0.505–0.885	
Sex				0.301
Male	83	0.712	0.612–0.812	
Female	25	0.577	0.105–1.049	
cT				0.002
cT1	23	0.957	0.873–1.041	
cT2	12	0.833	0.621–1.045	
cT3	36	0.765	0.622–0.908	
cT4	37	0.438	0.201–0.675	
Postoperative Chemo				0.003
Untaken	32	0.936	0.934–1.000	
Taken	76	0.660	0.559–0.772	
Histologic type				0.733
Adenocarcinoma	99	0.698	0.577–0.819	
Signet-ring cell carcinoma	7	0.714	0.379–1.000	
Special type	2	0	/	
Transmural involvement				<0.001
Negative	64	0.873	0.791–0.955	
Positive	44	0.410	0.149–0.671	
Numbers of LN (> 5 mm) in GBA				0.015
0	61	0.799	0.697–0.901	
≤ 2	28	0.610	0.247–0.973	
> 2	19	0.379	0.112–0.646	
Gastrophrenic ligament involvement				0.128
Negative	91	0.720	0.593–0.847	
Positive	17	0.601	0.346–0.856	
Diaphragm involvement				0.609
Negative	98	0.692	0.567–0.817	
Positive	10	0.800	0.553–1.047	
Perigastric fat involvement				0.086
Clear	36	0.861	0.747–0.975	
Blurring	53	0.564	0.358–0.770	
Obliteration	19	0.769	0.567–0.971	

cT clinical T stages; *pT* pathological T stages; *LN* lymph nodes

Follow up

Overall survival (OS) was measured from the preoperative CT examination date until gastric cancer-specific death, and patients alive or dead from other causes were censored at the last follow-up. The follow-up was conducted until Dec in 2017. The median follow-up time was 39.5 months, ranged from 5 to 87 months.

Statistical analysis

The agreement of judging all the CT findings between two raters was assessed using Kappa coefficient, 0–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80 and 0.81–1 indicated very poor, poor, moderate, substantial and excellent agreement, respectively. If the Kappa coefficient achieved substantial, one of the rater's evaluation result was taken for further analysis.

The following parameters from clinical information and preoperative CT were chosen as parameters for survival analysis: patient age (≤ 62 vs. > 62 years), sex (male vs.

female), cT staging, postoperative chemotherapy (untaken vs. taken), histologic type (adenocarcinoma vs. signet-ring cell carcinoma vs. special type), transmural involvement (negative vs. positive), numbers of swollen LN (short axis > 5 mm) in GBA (0 vs. ≤ 2 vs. > 2), gastrophrenic ligament involvement (negative vs. positive), diaphragm involvement (negative vs. positive), perigastric fat involvement (clear vs. blurring vs. obliteration).

The overall survival rate of the different parameters as well as the median survival time and survival curves were achieved by using the Kaplan–Meier method. Overall differences in the survival curves were analyzed with the log-rank test. The multivariate Cox proportional hazards model was used to adjust for the influence of prognostic factors.

All statistical analyzes and graphs were performed by using the Statistical Package for Social Sciences Program, version 22.0 (SPSS, Chicago, IL). For all analyzes, *P* values less than 0.05 was considered to denote a significant difference.

Results

Patients

Patients with pathological T3+ or lymph node metastasis positive were undertaken postoperative chemotherapy in our institution. The data was recorded. Histological type included adenocarcinoma, signet-ring cell carcinoma and special type, is also considered an important factor in the prognosis. Other characteristics which may be associated with the prognosis such as, sex, age, and the cT staging were recorded as well and listed in Table 1.

Kappa analysis

In diagnosis of the transmural involvement, diaphragm involvement, perigastric fat infiltration, lymph nodes in the GBA, gastrophrenic ligament involvement and cT staging, the two raters achieved excellent agreement, with Kappa coefficient of 0.962, 0.947, 0.924, 0.936, 0.999 and 0.948, respectively, *P* < 0.05.

Univariate survival analysis

There were 108 cases enrolled in this study. The results of univariate survival analysis were listed in Table 1. Univariate Kaplan–Meier estimates indicated that postoperative chemotherapy, transmural involvement, swollen lymph nodes in the GBA, and cT staging were prognostic factors associated with OS (*P* < 0.05). For the age and sex of patients, as well as histologic type and the other CT signs, there were no significant relation to the OS.

Multivariate survival analysis

Multivariate survival analysis was performed to determine the independent prognostic factors for PGC. Multivariate analysis by Cox proportional hazard model showed that the involvement of transmural, diaphragm and perigastric fat, as well as cT staging, were independent prognostic factors, which were showed in Table 2. The Kaplan–Meier curves of these prognostic factors on survival outcome were showed in Fig. 4.

Discussion

Much research concerning the spatial relationships among subphrenic spaces has been performed during gross anatomy [14–16]. An intimate knowledge of the anatomy and topographic relations of the proximal stomach is essential to understand the specifics of tumors at this location. The visceral peritoneum covers the gastric surface except a small postero-inferior area, near the cardiac orifice, where the stomach contacts the diaphragm at the reflexions of the gastrophrenic and left gastropancreatic folds. Gastric carcinoma characteristically progresses by local extension from the mucosa to the submucosa through the muscularis propria to subserosal tissue. From this point, tumors can spread via the subperitoneal spaces of various supporting peritoneal ligaments into adjacent organs. The GBA is not covered by the visceral peritoneum, there is no serosa in this small postero-inferior area. Cancers located in proximal stomach

Table 2 Independent predictors of GBA invasion in the multivariate Cox regression analysis

Prognostic factor	Hazard ratio ^a	<i>P</i> value
cT		
cT1	1	/
cT2	4.256 (0.367–49.405)	0.247
cT3	17.821 (1.276–248.897)	0.032
cT4	41.357 (2.747–622.591)	0.007
Transmural involvement		
Negative	1	/
Positive	8.194 (2.150–31.266)	0.002
Diaphragm involvement		
Negative	1	/
Positive	0.210 (0.042–0.986)	0.048
Perigastric fat involvement		
Clear	1	/
Blurring	0.125 (0.018–0.885)	0.037
Obliteration	0.020 (0.001–0.264)	0.003

cT clinical T stages; LN lymph nodes

^aNumbers in parentheses are 95% confidence intervals

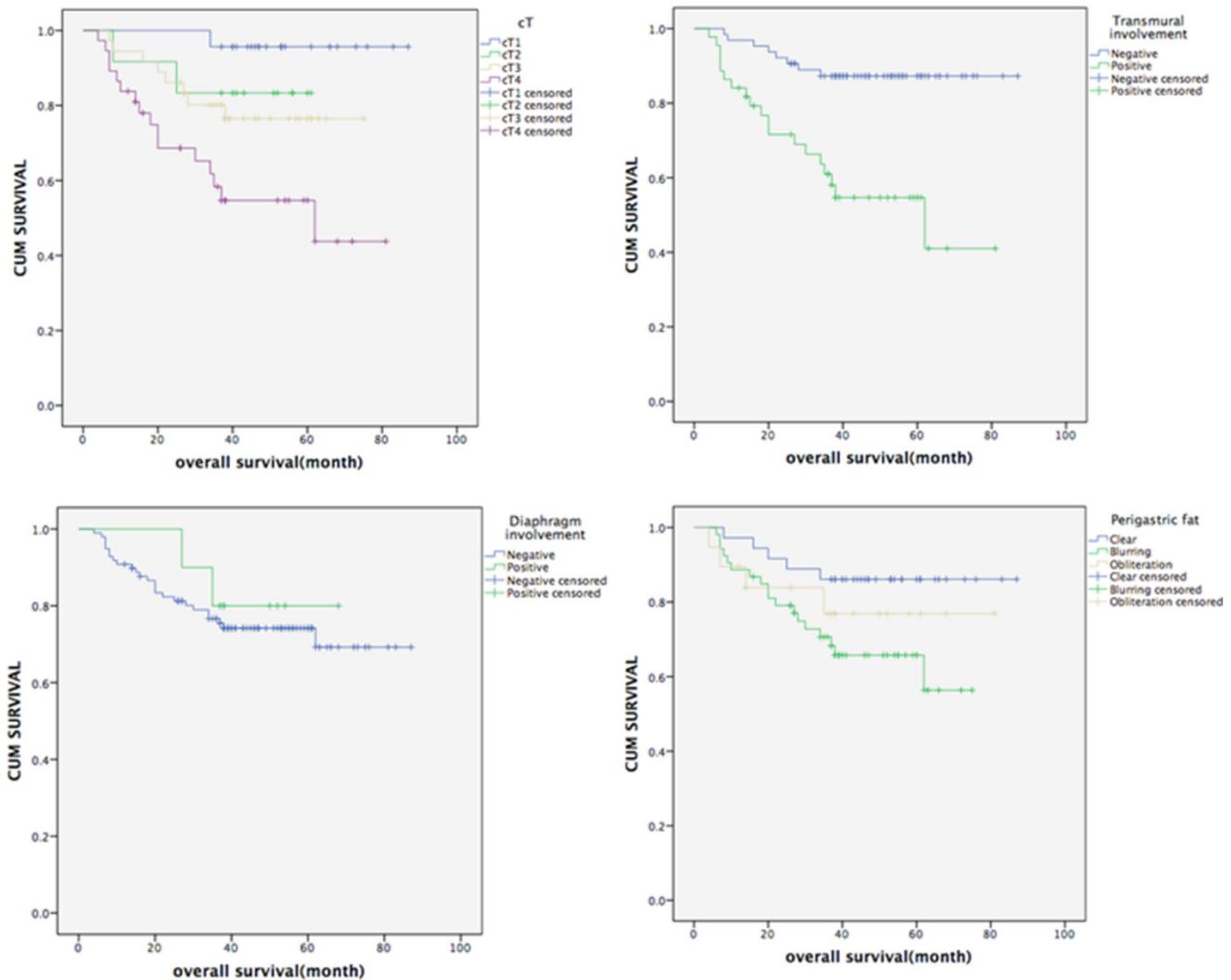


Fig. 4 The Kaplan–Meier curves of prognostic factors on survival outcome

can invade the GBA, subsequently, the retroperitoneal space [10].

It is well known that aggressiveness of gastric cancer depends on a number of factors, including wall invasion pattern and lymph node status, which are the two most important findings to estimate prognosis and to guide decision making. As in our study, transmural involvement and regional lymph node seen on CT were associated with OS. Another previous study also demonstrated that, the presence of regional lymph node metastases alone is the most important independent prognostic factor for survival in patients [17, 18].

In our study, muscles of gastric wall or left diaphragm were easily misdiagnosed as tumor extramural invasion when the subphrenic fat is too thin to be identified on CT imaging (Fig. 5). Further, the lack of normal extraperitoneal fat may not be a reliable sign of diaphragmatic invasion

because many of these patients are malnourished and have a paucity of intra-abdominal fat. Which can also explain the result that the diaphragm involvement showed significant relation to the OS in Multivariate analysis. Transmural invasion has a much higher emergence rate (40.7%) than diaphragm involvement (9.3%), which can explain the reason why the hazard ratio of transmural (8.194) and diaphragm (0.210) involvement was quite different. Furthermore, the thickness of the abdominal fat may be impact factor of the evaluation of transmural involvement and should be further researched.

Patients with pathological T3+ or lymph node metastasis positive were undertaken postoperative chemotherapy in our institution. Hence postoperative chemotherapy had not been chosen as parameters for multivariate survival analysis since it had strong correlation to T stage. Treatment of gastric cancer is multi-factorial, but surgery still plays a primary

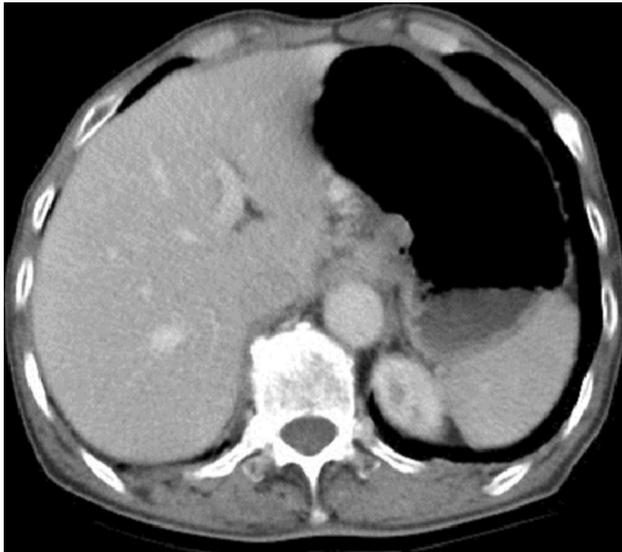


Fig. 5 Proximal gastric cancer (pT4) in a 71-year-old man. Axial CT shows transmural involvement with blurring and obliteration of the perigastric fat plane

role in management, since it is the only approach that can lead to cure. It is worth mentioned that lymph nodes in GBA are in deep and insidious position. Because of the anatomic situation, the classification of lymph node metastases of proximal third tumors deserve special attention. The partial extraperitoneal location of the proximal stomach allows lymphatic spread frequently toward the GBA [10]. The current version of the TNM classification does not take this specific situation into account when treating those tumors. A prognosis-dependent procedure should therefore be adapted for the removal of retroperitoneal lymph nodes.

Our study has several limitations. First, the evaluation of CT signs may be subjective. During the evaluation, an irregular tumor contour with only a few small linear strands of soft tissue extending into the fat plane was defined as transmural involvement. A fat stranding involving more than one-third of the tumor borders was defined as representative of an involvement or penetration of the subphrenic fat layer. Second, we did not perform a one-to-one correlation of pathological results. Third, the retrospective design induced selection bias.

In conclusion, CT findings of GBA invasion in patients with PGC, not only the direct sign of transmural involvement but also the indirect signs such as the infiltration of diaphragm and perigastric fat may be independent prognostic factors potentially, which could be of aid in the selection of treatment, and should be given more emphasis in future clinical practice.

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Author contributions Y-SS is acting as the guarantor of the article, and was responsible for the study design and for preparation of the manuscript. R-JS and LT were responsible for the study design and data collection. X-TL and Z-YL were responsible for development of methodology. All co-authors had input into study design, conduct, data analysis or interpretation. All co-authors critically reviewed the manuscript, and necessary revisions were made to accommodate their suggestions and opinions.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical statement This retrospective study was approved by the institutional review board of our institute, and the requirement of informed consent was waived.

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