Japanese Journal of Radiology (2019) 37:817–825
https://doi.org/10.1007/s11604-019-00887-3

ORIGINAL ARTICLE

Usefulness of histologic differences and perivascular infiltration for preoperative T staging of advanced gastric cancer using computed tomography

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Received: 11 August 2019 / Accepted: 7 October 2019 / Published online: 17 October 2019

Abstract

Purpose This study aimed to determine whether histologic differences and perivascular infiltration are useful for clinical T staging of advanced gastric cancer (AGC).

Materials and methods This retrospective study included 160 patients with pathologically confirmed AGC who had available preoperative stomach computed tomography (CT). Using stomach CT, they were classified according to standard T stage, histologic T stage, and perivascular T stage. Accuracy of each T stage criteria was analyzed. Perivascular infiltrations for the evaluation of prognosis were correlated with time to tumor progression by log-rank test.

Results There was a significant difference between the accuracies of the standard and histologic T stages ($p < 0.001$), whereas there was no significant difference between the standard and perivascular T stages ($p = 0.07$). In 121 patients who were pathologically confirmed as having T3 or T4a tumor, there was a significant difference between the standard and perivascular T stage ($p < 0.001$). In patients having T3 or T4a tumor, time to tumor progression of the negative perivascular infiltration subgroup was significantly longer than the positive subgroup.

Conclusion Consideration of histologic differences and perivascular infiltration may be useful for clinical T staging of AGC.

Keywords Computed tomography · Gastric cancer · Histology · Perivascular infiltration · Staging

Introduction

Gastric cancer is the fourth most common cancer and has high incidence in Asia [1, 2]. Early detection and accurate preoperative staging are essential pretherapeutic approaches to reduce mortality.

In gastric cancer, despite advances in medical treatment, surgical resection continues to be the primary modality for complete locoregional control [3]. Laparoscopy-assisted distal gastrectomy (LADG) was developed as a minimally invasive surgical option for gastric cancer and was clinically implemented to treat early gastric cancer (EGC) [3]. On the other hand, open D2 lymphadenectomy (ODG) is the surgical procedure performed to treat advanced gastric cancer (AGC). Therefore, LADG is generally performed in cases of EGC, and open D2 distal gastrectomy (ODG) is performed in cases of AGC.

Several studies recently showed that the overall survival and disease-free survival rates following LADG and ODG are not significantly different [3, 4]. One study showed that the compliance rate was not different between LADG and ODG, especially in patients with clinical stages IB and II of gastric cancer [3]. Therefore, in addition to EGC, LADG with D2 lymphadenectomy is a feasible treatment option for AGC [5–8].

Accurate preoperative staging is an important step for selecting of optimal surgical treatment options. T and N stages are determining factors in deciding the treatment for AGC. However, the accuracy of computed tomography (CT) for the estimation of lymph node metastasis (N stages) in patients with gastric cancer remains poor, i.e., about 66.1% [9]. Therefore, this study focuses on the accuracy of determining preoperative T stage. Endoscopic ultrasound (EUS)

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is a more accurate modality for determining preoperative T stage [10]. However, CT imaging technologies are evolving, and the increasing resolution of CT images, multiplanar reformation, and use of contrast suggest comparable accuracies between CT scan and EUS [11]. Based on histologic differences, undifferentiated carcinoma (poorly differentiated adenocarcinoma and signet ring cell carcinoma) could still influence preoperative T staging because it is associated with the risk of invasion and metastasis [12, 13]. Differentiation between stages T3 and T4a using CT scan is difficult because of the poor delineation of the gastric serosa. Thus, it appears that histologic and perivascular morphologic features may be helpful in determining the accuracy preoperative T stage on CT.

This study aimed to determine whether histologic and perivascular morphologic features of AGC on CT images are useful for clinical T staging.

Materials and methods

This retrospective study was approved by our institutional review board and all procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The requirement for informed consent was waived because it was a retrospective study.

Patients

Review of medical records from December 2009 to December 2016 yielded 1204 patients in our hospital who had biopsy-proven gastric cancer. Out of the 1204 patients, 1044 patients were excluded for the following reasons: (1) unavailable stomach CT for review such as general abdomen CT (no stomach distension) or none ($n=648$), (2) did not undergo surgery in our hospital ($n=72$), (3) had pathologically confirmed early gastric cancer or other tumor types ($n=323$), and (4) stomach CT images had severe motion artifact ($n=1$). Excluding these 1044 patients, 160 patients were finally enrolled in this retrospective study (Table 1). The mean patient age was 64.5 years (range 27–89 years), and the study cohort comprised 116 male (mean age 64.7 years; range 35–89 years) and 44 female (mean age 65.3 years; range 27–86 years) patients. The mean interval between the preoperative stomach CT and surgery was 4.4 days (range 2–30 days).

CT protocol

Two scanners were used to obtain the required stomach CT images: a 64-channel multidetector CT (MDCT) scanner (Aquilion 64; Toshiba Medical System Co., Tokyo, Japan) for 82 patients and a 128-channel MDCT (Somatom Definition Flash; Siemens Medical Systems, Forchheim, Germany) scanner for 78 patients. The following MDCT parameters were used for the two scanners: (1) 64-MDCT scanner with collimation 64 × 0.5 mm; pitch 0.828, and rotation time 0.6 s; (2) 128-MDCT scanner with collimation 128 × 0.625 mm; pitch 0.8, and rotation time 0.5 s. The kilovoltage and effective tube current time charge were 120 kV and 200–250 mAs, respectively. In our study, before the CT procedure, oral contrast medium (500–1000 mL of tap water) was administered to each patient immediately on the CT table to achieve gastric distention. After a fasting period of over 6 h, each patient received an intravenous dose (2 mL/kg; total volume < 150 mL) of nonionic contrast material (Ultravist 300; Schering, Berlin, Germany). The following CT phase protocol was used: after unenhanced CT, portal venous phase images were obtained 60–70 s after contrast injection. All imaging, were performed during deep inspiration. For axial and coronal images, 3-mm thin sections and 3-mm reconstruction interval images were reconstructed for clinical interpretation.

Table 1 Baseline characteristics of enrolled patients with advanced gastric cancer

Clinicopathologic findings	Number
Age (years, mean, range)	64.5 (27–89)
Sex (male:female)	116:44
Pathologic T stage	
T2	39
T3	30
T4a	91
Pathologic type	
MD	66
PD	69
SRC	14
PD + SRC	7
Others[a]	4
Treatment option	
Partial gastrectomy	113
Total gastrectomy	43
Sleeve	4

SD standard deviation, *MD* moderate differentiation, *PD* moderate differentiation and poor differentiation or only poor differentiation, *SRC* signet ring cell

[a]Others: carcinoma of lymphoid stroma

Image analysis

Individual review of the stomach CT images was subsequently performed by two experienced radiologists with 14 and 3 years of clinical experience in CT image interpretation, respectively. They knew that the patients had been referred for evaluation of gastric cancer but were blinded to all other information including the patients' detailed medical history, laboratory results, and previously assigned tumor stage.

Two radiologists independently reviewed the stomach CT images and assessed the T stage based on standard, histologic, and perivascular T stage in the stomach CT images. Differences in their assessments were resolved consensually by mutual discussion.

The tumor stage assessed using the standard criteria was called the standard T stage. As per the standard criteria [12], T2 tumors show loss of low-attenuated stripes indicating involvement of the entire submucosal layer. T3 tumors have subserosal invasion, and visual discrimination between a gastric mass and the outer layer is not possible. In addition, a smooth outer margin of the outer layer or a few small linear strandings in the perigastric fat plane can be noted. T4a tumors frequently show micronodules or dense, band-like stranding, and can be found in the perigastric area. We focused mainly on T3 and T4a tumors in our analysis.

We considered two stages based on the standard T stage: (1) histologic T stage was based on the pathological report obtained by endoscopic biopsy. If the histologic difference was confirmed as undifferentiated carcinoma (poorly differentiated adenocarcinoma or signet ring cell carcinoma), standard T stage was one step overestimated for the histologic T stage. Mixed-type gastric carcinomas, which comprised of non-homogeneous mixtures of differentiated and undifferentiated carcinomas, were classified into undifferentiated carcinoma and one step overestimated for the histologic T stage [13–15]. For example, a standard T stage T2 or T3 with undifferentiated carcinoma was considered as histologic T stage T3 or T4a, respectively; (2) perivascular T stage was based on perivascular infiltration, defined as soft tissue with low attenuation surrounding the vessels that were inserted within or passed around the stomach wall. Usually, perigastric fat strandings can mimic the cancer infiltration out of the serosa and lead to the overstaging of T3 tumors [16]. In this study, perivascular infiltration referred to specific perigastric fat strandings along perigastric vessels that may reflect microscopic invasion to serosa that could potentially cause underestimation. If perivascular infiltration was present in the stomach CT images, the standard T stage was overestimated for the perivascular T stage. For example, the standard T stages of all T2 and T3 showing perivascular infiltration were considered as perivascular T stage T4a.

The postoperative specimens underwent histopathological analysis for the depth of invasion of the gastric wall according to the T stage based on the pathologic TNM staging system developed by the 7th American Joint Committee on Cancer and the International Union Against Cancer [17]. The result of this approach was considered as a pathologically confirmed T stage.

Accuracies of the standard, histologic, and perivascular T stage were analyzed and compared with the pathologically confirmed T stage. In patients having T3 or T4a tumor, perivascular infiltration was correlated with time to tumor progression (TTP), from the first follow-up CT after surgery until either tumor recurrence or distant metastasis diagnosed using CT scan, magnetic resonance imaging, positron emission tomography, or esophagogastroduodenoscopy imaging. We compared the time to tumor progression between the positive subgroup having perivascular infiltration and the negative subgroup not having perivascular infiltration for prognosis.

Proof of tumor

The pathologic proof of all tumors was obtained after gastric surgery, which included partial gastrectomy ($n = 113$), total gastrectomy ($n = 43$), or sleeve gastrectomy ($n = 4$). The 156 patients examined had a total of 156 confirmed adenocarcinomas (moderately differentiated, 66; poorly differentiated, 69; poorly differentiated with signet ring cell, 7; signet ring cell, 14), and carcinoma with lymphoid stroma was confirmed in 4 patients. The specimens from these patients were histologically analyzed for the depth of invasion of the gastric wall (Table 1). In the 160 patients, 39 tumors were classified as T2, 30 as T3, and 91 as T4a, according to the T stage based on the pathologic TNM staging system developed by the 7th American Joint Committee on Cancer and the International Union Against Cancer [17].

Statistical analysis

The numbers and percentages of continuous variable data are expressed as mean ± standard deviation (SD). The accuracies of the standard, histologic, and perivascular T stages were calculated according to the pathologic T stage group. The McNemar test was used to determine statistical significance of differences among the preoperative T stages (standard, histologic, and perivascular T stage). A TTP curve was generated using the Kaplan–Meier method, and differences were evaluated with the log-rank test. The interobserver agreements for the confidence ratings of standard, histologic, and perivascular T stage were analyzed with kappa statistics (kappa values: ≤ 0.40, = poor agreement; 0.41–0.74, = moderate/good agreement; ≥ 0.75, = excellent agreement). All statistical tests were performed using SPSS software (version 25.0, SPSS Inc, Chicago, IL). The results were considered statistically significant if the p value was less than 0.05.

Results

All gastric lesions were detected by the readers and were suitable for imaging analysis. The comparison between the pathologic T stage and the three clinical CT T stages is summarized in Table 2. Overall accuracies of the standard, histologic, and perivascular T stages were 65%, 77.5%, and 68.8%, respectively. The standard T stage showed the highest accuracy for T2 tumor stage. Perivascular T stage and histologic T stage showed the highest accuracy for T3 tumor stage and T4 tumor stage, respectively. Comparison of the accuracies of the three clinical CT T stage criteria in all AGC groups is shown in Table 3. There was a significant difference between the accuracies of the standard and histologic T stages ($p < 0.001$; Fig. 1).

Table 2 Accuracy of each T stage for determining the pathological T stage in patients with advanced gastric cancer

T stage	Pathologic T stage			Accuracy (%)[a]
	pT2 ($n = 39$)	pT3 ($n = 30$)	pT4 ($n = 91$)	
Standard T stage				
T2	29	9	0	74
T3	9	17	33	57
T4	1	4	58	64
Histologic T stage				
T2	25	3	0	64
T3	12	20	12	67
T4	2	7	79	87
Perivascular T stage				
T2	20	5	0	51
T3	8	17	18	77
T4	11	8	73	75

[a]The overall accuracy of the standard T stage was 65%, while that of the histologic T stage and perivascular T stage was 77.5% and 68.8%, respectively

Table 3 Concordance between each clinical T stage and the pathologically confirmed T stage in all patients with advanced gastric cancer ($n = 160$)

	Standard T stage		p value
	Concordant[a]	Discordant[b]	
Histologic T stage			
Concordant	96	28	< 0.001
Discordant	8	28	
Perivascular T stage			
Concordant	103	7	0.07
Discordant	1	49	

[a]Concordant: number of cases showing concordance between each T stage and the pathologically confirmed T stage

[b]Discordant: number of cases showing mismatch between each T stage and the pathologically confirmed T stage

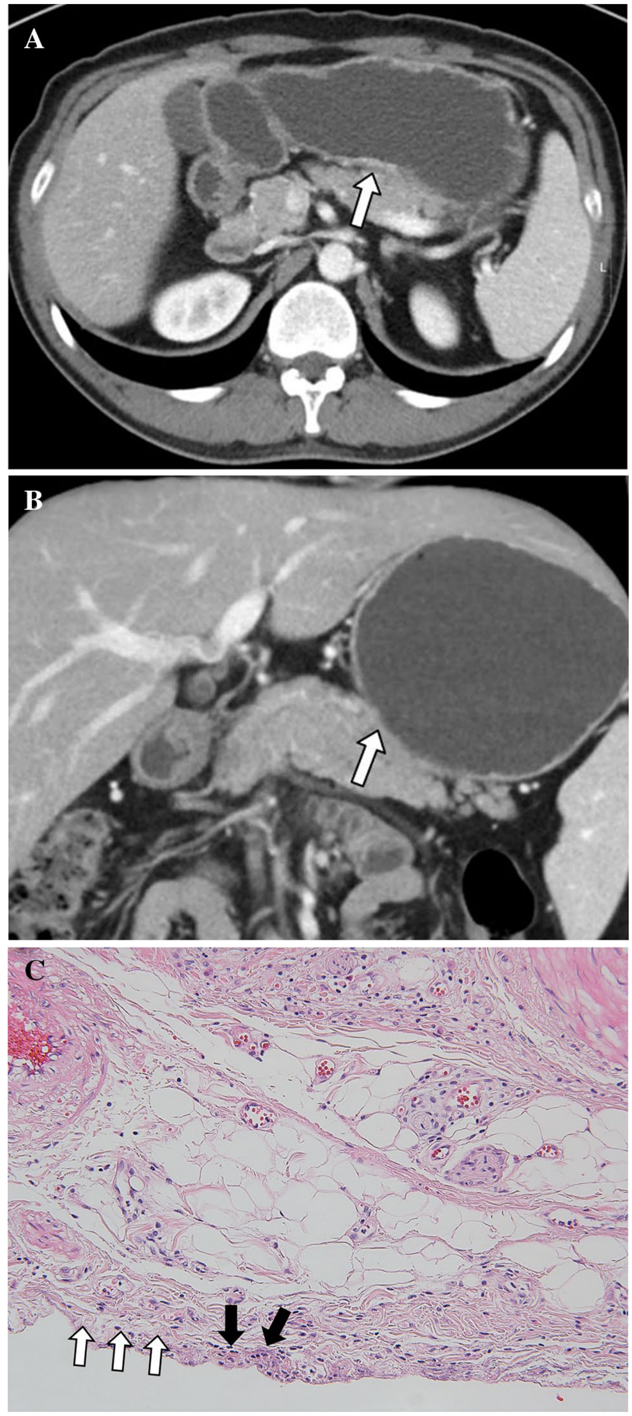

Fig. 1 Representative case involving a 48-year-old male with poorly differentiated adenocarcinoma of the stomach. Axial (**a**) and coronal (**b**) computed tomography (CT) images of the stomach show mural wall enhancement in the posterior wall of the stomach below the middle part of the body (arrow), with some perigastric fat infiltration. The standard, histologic, and perivascular T stages are T3, T4a, and T3, respectively. **c** A photomicrograph (hematoxylin and eosin staining, ×200) reveals tumor cells (black arrow) invading the serosa (white arrow). The pathologically confirmed stage is T4a

Table 4 Accuracies of the standard T stage and perivascular T stage, determined by computed tomography, in the T3 and T4a gastric cancer groups ($n = 121$)

	Standard T stage		p value
	Concordant[a]	Discordant[b]	
Perivascular T stage			
Concordant	74	16	< 0.001
Discordant	1	30	

[a]Concordant: number of cases showing concordance between each T stage and the pathologically confirmed T stage

[b]Discordant: number of cases showing mismatch between each T stage and the pathologically confirmed T stage

However, no significant difference was found between the accuracies of the standard and perivascular T stages ($p = 0.07$). Ten of the 39 pathologically confirmed T2 tumors were overestimated because of false-positive perivascular infiltration findings. Inflammatory lesions, such as ulcer, which are mixed in the cancer lesion, can often be mistaken for perivascular infiltration [18–20]. Separately, accuracy of the pure histologic T stage, which was only defined as poorly differentiated adenocarcinoma except mixed type gastric carcinoma and signet ring cell carcinoma, was 82.1%. However, no significant difference was found between the accuracies of the histologic and pure histologic T stages ($p = 0.004$).

Among all AGC groups, 121 patients who were pathologically confirmed with T3 or T4a tumors were categorized into T3 and T4a groups. Accuracies of the standard and perivascular T stages in the T3 and T4a groups are shown in Table 4. Accuracy of the perivascular T stage (74.4%) was significantly superior to that of the standard T stage (62%; $p < 0.001$; Fig. 2).

Among 30 patients with pathologically confirmed T3 tumors, four patients showed perivascular infiltration (Fig. 3). Endoscopically, these patients showed the ulcero-infiltrative type lesions and, moreover, perivascular infiltration indicated inflammation and not cancer. Of the 91 patients with pathologically confirmed T4a tumors, 51 showed perivascular infiltration. The distribution of tumors according to the presence or absence of perivascular infiltration was significantly different between the pathologically confirmed T3 and T4a tumor groups (Table 5). In total, 55 patients with T3/T4a stage tumors showed perivascular infiltration and were classified as the positive subgroup, whereas 66 patients without perivascular infiltration were classified as the negative subgroup. The perivascular negative group exhibited a significantly longer TTP (duration, 1–88 months; mean, 30 months) than the positive group (duration, 1–83 months; mean, 23 months; $p < 0.01$; Fig. 4).

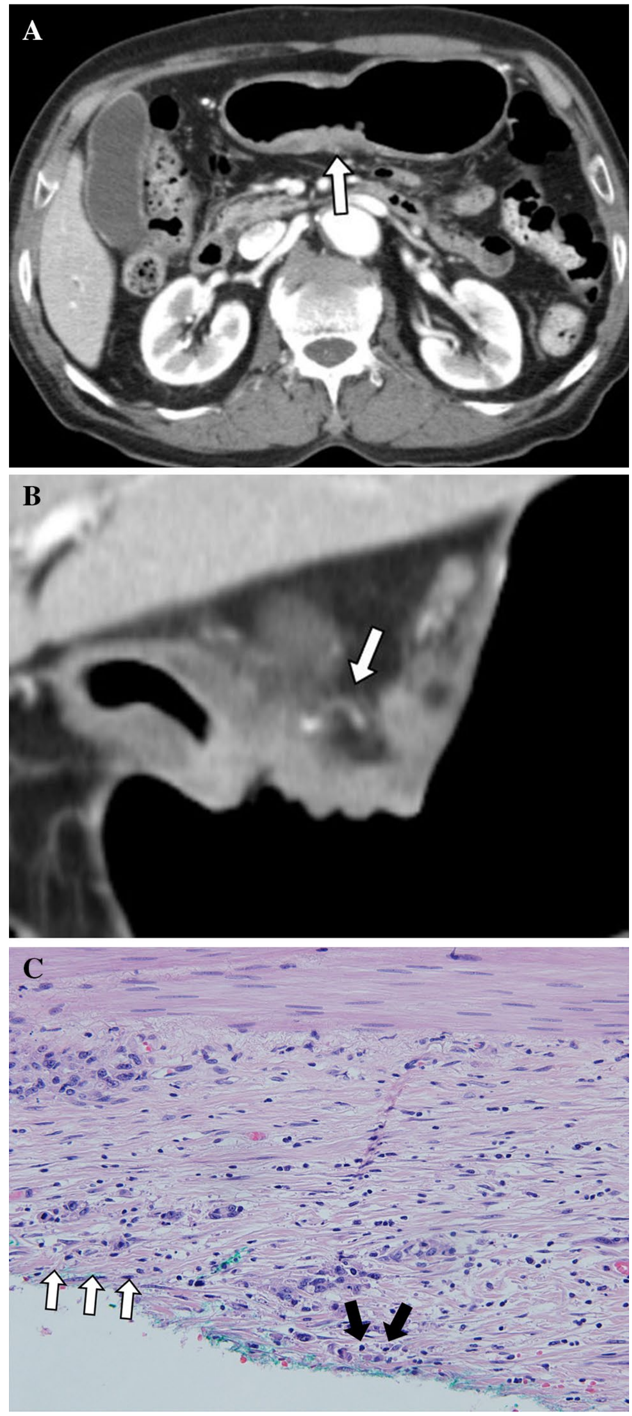

Fig. 2 Representative case involving a 58-year-old male with moderately differentiated adenocarcinoma of the stomach. **a** An axial computed tomography (CT) image of the stomach shows an ulcero-infiltrative lesion at the proximal antrum (lesser curvature; arrow), with mild perigastric fat infiltration. **b** A coronal CT image shows perivascular infiltration (arrow). The standard, histologic, and perivascular T stages are T3, T3, and T4a, respectively. **c** A photomicrograph (hematoxylin and eosin staining, ×200) reveals tumor cells (black arrow) invading the serosa (white arrow). The pathologically confirmed stage is T4a

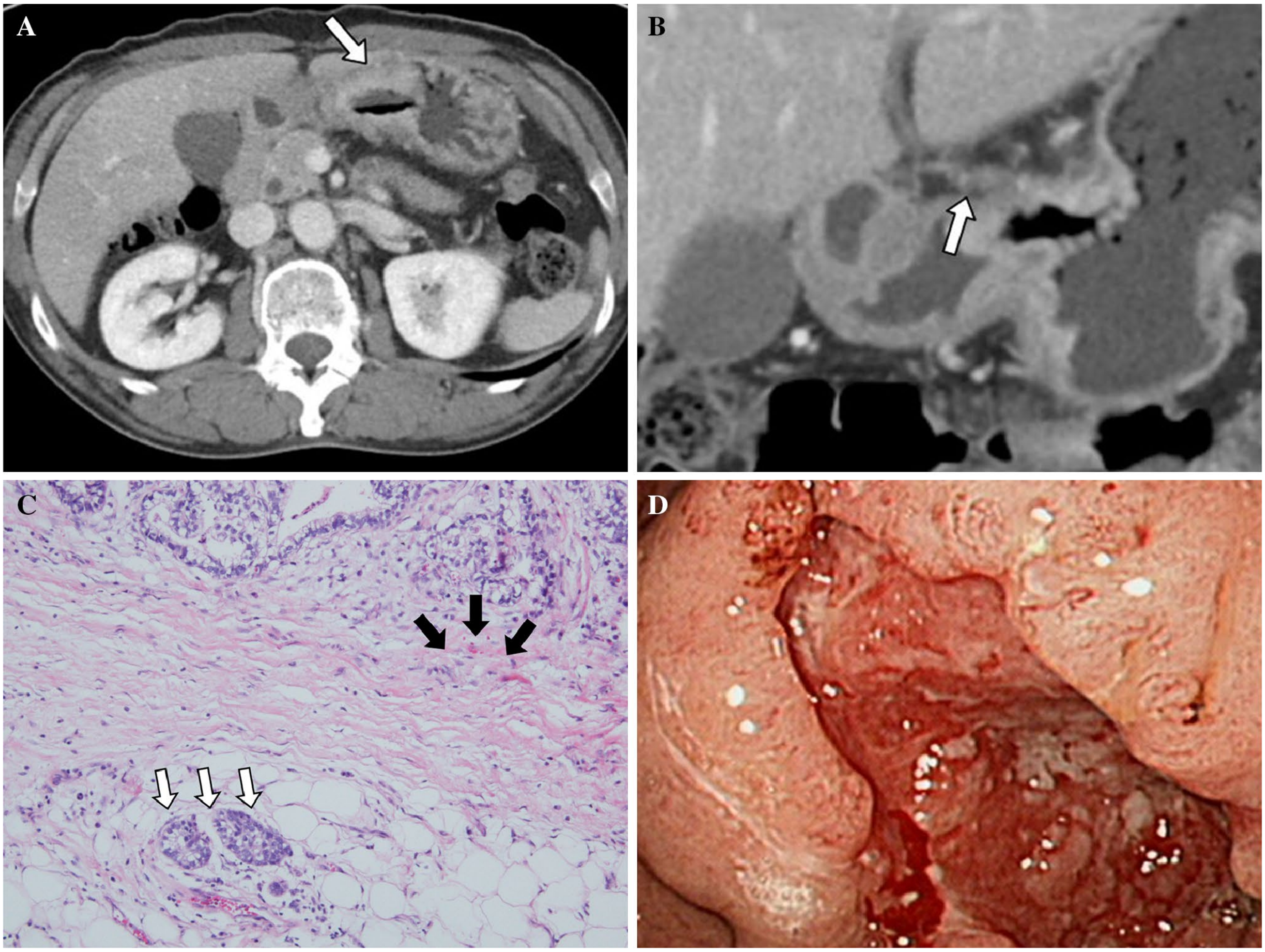

Fig. 3 Representative case involving a 60-year-old male with poorly differentiated adenocarcinoma of the stomach. **a** An axial computed tomography (CT) image of the stomach shows an ulcero-infiltrative lesion at the stomach angle (arrow), with perigastric fat infiltration. **b** A coronal CT image shows perivascular infiltration (arrow). The standard, histologic, and perivascular T stages are all T4a. **c** A photomicrograph (hematoxylin and eosin staining, ×100) reveals tumor cells (black arrow) penetrating the subserosal connective tissue with perineural invasion (white arrow). There is no serosal invasion. The pathologically confirmed stage is T3. **d** Endoscopy shows an ulcero-infiltrative mass, which may cause false-positive observations of perivascular infiltration

Table 5 Distribution of T3 and T4a tumors according to the presence or absence of perivascular infiltration ($n = 121$)

	Perivascular infiltration		*p* value
	Positive[b]	Negative[c]	
T stage[a]			
T3 ($n = 30$)	4/30	26/30	0.006
T4a ($n = 91$)	51/91	40/91	

[a]T3 and T4a are the pathologically confirmed T stages

[b]Positive = perivascular infiltration was present

[c]Negative = perivascular infiltration was absent

The interobserver agreements for the standard, histologic, and perivascular T stages were excellent, with kappa values ranging from 0.84 to 0.89.

Discussion

The mural invasion of gastric cancer into the gastric wall has been classified according to the TNM classification [15]. In the standard CT criteria for determining the T stage, clinical T3 stage (indicative of subserosal invasion) is defined by the inability to discriminate between a gastric mass and the outer layer, a smooth outer margin of the outer layer, or a few visible small linear strandings in the perigastric fat plane. Clinical T4a stage shows micronodules or band-like stranding in the perigastric area [15]. It is nevertheless difficult to distinguish between T3 and T4a stages tumors because of the following reasons: first, poor visualization of the gastric serosa in CT images and second, individual variation in the amount of subserosal adipose tissue. Vascular structures of perivascular infiltrations are blood vessels running

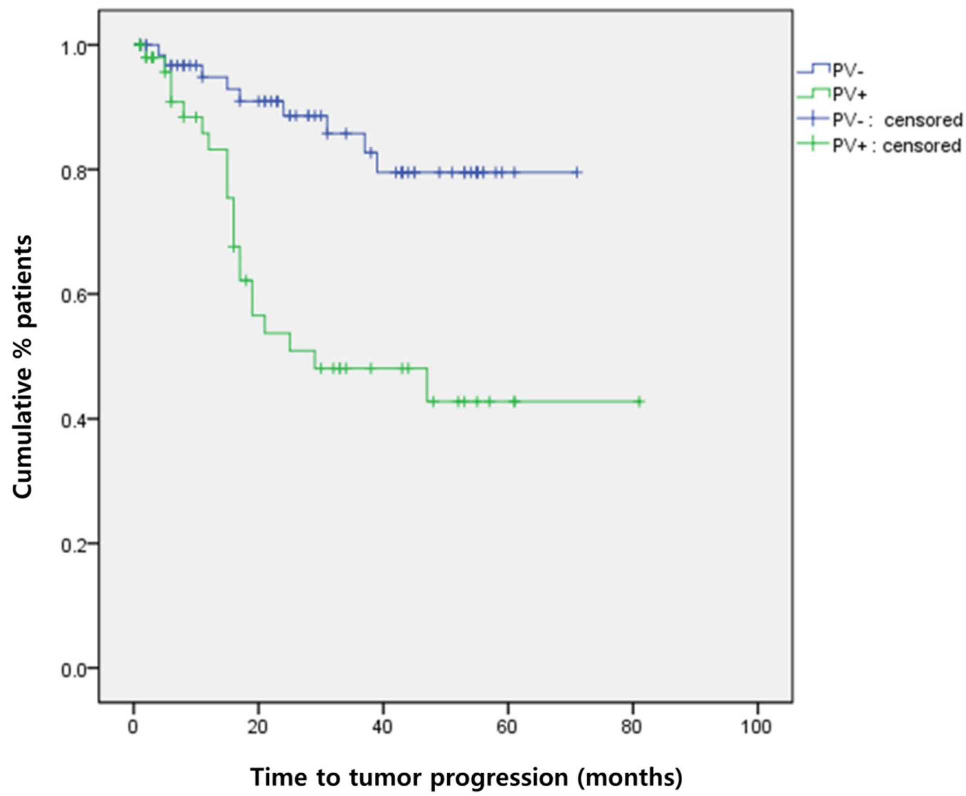

Fig. 4 The time to tumor progression in patients with pathologically confirmed T3 and T4a tumors. The long-term prognosis (up to 83 months) is significantly different between the positive perivascular infiltration (PV+) group and negative perivascular infiltration group (PV−; $p < 0.001$)

through bundles of fat between the parietal and visceral peritoneum. The omentum serves as a conduit for blood vessels. We hypothesized that perivascular infiltrations are a predisposing factor for aggressive tumor extension, which implies tumor invasion of blood vessels. Although the perivascular T stage was not significantly different among all AGC groups as compared to the standard T stage, the difference in perivascular T stage in the T3 and T4a groups was statistically significant. In the T3 and T4a groups, the TTP was shorter (indicative of a poor prognosis) in the positive perivascular infiltration subgroup than in the negative perivascular infiltration subgroup. Therefore, we suggest that considering the perivascular infiltration increases the accuracy of T staging.

Undifferentiated carcinomas, including poorly differentiated adenocarcinoma or signet ring cell carcinoma, have distinctive growth patterns [21]. Unlike differentiated adenocarcinoma, the signet ring cell carcinomas have decreased expression of E-cadherin, which is associated with cell-to-cell adhesion, and consequently, the cells do not adhere to each other [22]. Moreover, E-cadherin deficiency leads to migration of tumor cells and invasion of adjacent tissues [23]. Gastric cancers also showed different enhancement patterns on multiphasic contrast-enhanced CT depending on their histologic type [24, 25]. Therefore, signet ring cell carcinomas have been associated with lateral tumor extension whereas poorly differentiated adenocarcinomas have been associated with vertical tumor extension [21]. The rate of lymphovascular invasion was also higher in poorly differentiated adenocarcinomas than in signet ring cell carcinoma, although this difference was not statistically significant [21]. According to our findings, the histologic T stage was significantly different for the T stage of AGC compared to the standard T stage due to the histologic characteristics of aggressive tumor extension. Therefore, we also suggest that inclusion of histologic differences in the diagnostic evaluation increases the accuracy of T staging.

Our study has some limitations. First, the retrospective study design limits our study. In addition, potential selection bias might have been present toward patients with less-advanced disease because all the patients we recruited had surgically confirmed AGC. Second, the sample size was small because the study was conducted over a relatively short period and in a single institution. Third, because the target vessels (with regard to perivascular infiltration) are often narrower than 2–3 mm, the slice thickness and increment should at least be 1mm/1mm, especially in coronal multiplanar reconstruction image. However, we could not verify this because of the retrospective design and no raw data were available for reconstruction. Moreover, as per the guideline for stomach CT, 3-mm-thin section is generally recommended for diagnostic gastric cancer detection [26, 27]. Axial and coronal

CT images were reconstructed using 3mm slice thickness and increment. Further studies are needed to evaluate the target vessels in terms of perivascular infiltration with reconstructed CT images using 1mm slice thickness and increment. Fourth, only axial and coronal images of stomach CT were used, without EUS or CT gastroscopy to aid in the determination of T stage. Fifth, assessment of histologic T stage using with endoscopic biopsy may have been overestimated in some biopsy results that indicated small (or suspected) undifferentiated carcinoma. Sixth, the presence of perivascular infiltration in CT images was interpreted subjectively by the two reviewers. Thus, overestimation of clinical T stage because of perigastric inflammation is possible. However, the interobserver agreement was excellent, and a conclusion was achieved with sufficient consensus for discrepancies.

In conclusion, considering the histologic differences and perivascular infiltration may be a useful option to demonstrate AGC aggressiveness and could influence clinician's decision for preoperative CT T staging. Notably, perivascular infiltration could be a more useful factor for differentiating T3 and T4a gastric cancers.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JYK and W-SC. The first draft of the manuscript was written by JYK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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