ORIGINAL ARTICLE

Preoperative T staging of colon cancer using CT colonography with multiplanar reconstruction: new diagnostic criteria based on "bordering vessels"

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Abstract

Purpose Preoperative T staging of colon cancer, in particular, for distinguishing T3 from T2 and T4, has been a challenge. The aim of this study was to evaluate newly developed criteria for preoperative T staging of colorectal cancer using computed tomography colonography (CTC) with multiplanar reconstruction (MPR), based on the spatial relationship of tumors and "bordering vessels," that is, marginal vessels that are detectable by multi-detector row CT with MPR.

Methods A total of 172 patients with colon and upper rectal cancer who underwent preoperative CTC and surgery between August 2011 and September 2013 were included. Preoperative T staging using the new criteria was performed prospectively and compared with pathologic results.

Results Sensitivity, specificity, and accuracy of T staging by CTC using the new criteria were 63%, 80%, and 77% for T2 ($n = 30$); 72%, 94%, and 81% for T3 ($n = 95$); and 79%, 99%, and 97% for T4a ($n = 14$), respectively. Positive predictive value for T3 was 93%, indicating that a T3 diagnosis by CTC is precise. In addition, negative predictive value for pathological T4a was 98%, indicating that a "not T4a" diagnosis by CTC is also precise.

Conclusions Our newly developed criteria are useful for preoperative T staging, particularly for distinguishing T3 from T2 and T4.

Keywords Preoperative T staging · CT colonography · Multiplanar reconstruction (MPR) · Colon cancer

Introduction

In advanced colorectal cancer, differentiating T3 tumors from T2 and T4 tumors [1] is important because preoperative staging occasionally alters surgical strategy such as the extent of lymph node dissection, decision of surgical approach (laparoscopic or open), and application of preoperative chemotherapy. Indeed, preoperative staging differs: T2N0 is stage I, whereas T3N0 and T4N0 are stage II. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, surgical strategies such as the extent of lymph node dissection differ between T2 and T3/T4 in Japan [2]. Moreover, preoperative staging of "T4 or not" would allow physicians to select laparoscopic surgery as appropriate. The subgroup analysis of a recent trial (JCOG0404) that evaluated laparoscopic versus open complete mesocolic excision (CME) revealed that one factor associated with the unfavorable long-term outcome of laparoscopic surgery for stage II/III colorectal cancer was T4, suggesting that careful consideration must be given as to whether to operate laparoscopically on patients with T4 disease [3, 4]. Accurate preoperative T staging is also important for conducting clinical trials for locally advanced colon cancer such as FOxTROT trial (UK) [5], Prodige22-ECKINOXE trial (France) [6], and NCT01918527 trial (Denmark, Norway, Sweden), all of which investigate the merit of preoperative chemotherapy. Inclusion criteria of these three trials are high-risk T3 and T4 colon cancer.

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In order not to over-treat patients that do not require antineoplastic treatment, lessening the number of false-positive patients is strongly required for these trials.

The introduction of multi-detector row CT (MDCT) allowed faster scanning, thinner slices, reduced partial-volume artifacts, increased spatial resolution, and better image quality for both axial and multiplanar reconstruction (MPR) images [7]. Moreover, CT colonography (CTC) with MPR and three-dimensional (3D) images enables more accurate thin slice images, optional images, and detection of the spatial relationship between tumors and marginal vessels. For very lower rectal cancer, we recently reported that CTC with MPR, with an arbitrary selection, could be aligned to the tumor axis and better demonstrated tumor margins consecutively including the deepest section of the tumor [8]. CTC with MPR may overcome the issue of overstaging T2 tumors which remains unsolved even by magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) for lower rectal cancer [9, 10].

For colon cancer where serosa exists, preoperative T staging, particularly distinguishing T3 from T2 and T4, is also challenging [11–13]. The present study refers to marginal vessels, which comprise peripheral vessels, tumor-feeding vessels, and new blood vessels produced by tumor angiogenesis, which are detectable by MDCT with MPR at the subserosal layer as "bordering vessels." That is, the bordering vessels are marginal vessels at the subserosal layer in MPR images. These vessels reside in rich adipose tissue in the subserosal layer. We hypothesized that tumor-related alterations of the normal bowel contour and morphology of "bordering vessels" can serve as staging criteria. Specifically, tumors that do not involve bordering vessels and have a smooth outer border are considered T2, those with a rough border T3, and those that involve bordering vessels T4. This study introduces new diagnostic criteria for T staging by CTC with MPR and assesses their sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

Method

Patients

Between August 2011 and September 2013, 172 consecutive patients with colon and upper rectal carcinoma (96 males and 76 females; age range, 28–80 years; 172 lesions) who underwent preoperative CTC and surgical resection at our hospital were prospectively included in this study according to inclusion criteria (i.e., histopathologically confirmed colorectal adenocarcinoma). Patients with lower rectal cancer were excluded because the lower rectum lacks serosa and T4a does not apply to the lower rectum. Patients who received preoperative radiotherapy and/or chemotherapy, as well as those with

T4b or Tis tumors, were excluded. Patients provided written informed consent and underwent CTC on the same day as conventional colonoscopy. Biopsies subsequently confirmed the presence of colorectal adenocarcinoma. All patients underwent surgical resection within 1 month of CTC examination. This study was approved by the National Cancer Center Hospital Institutional Review Board (IRB) (IRB code: 2015-032).

CT colonography

CTC procedures have been described previously [14, 15]. Patients underwent MDCT using an intravenous contrast medium immediately after total colonoscopy without stool tagging. Thus, each patient received a bowel preparation in the form of polyethylene glycol solution (Niflec[R]; EA Pharma Co., Tokyo, Japan) before colonoscopy. Before the CTC procedure, an antiperistaltic agent (20 mg scopolamine butylbromide) was intramuscularly administered and an enema tube inserted into the rectum in the left lateral decubitus position. Patients received automated carbon dioxide (PROTOCO2L Insufflator[R]; Bracco Diagnostics Inc., NJ, USA). The enema tube remained in the rectum during examination. Initially, CTC was performed with patients in the prone position. The procedure was subsequently repeated with patients in the supine position.

CTC was performed with an 80× multi-detector CT scanner (Aquilion Prime, Toshiba Medical Systems, Tochigi, Japan). Scans were obtained through the abdomen and pelvis using the following parameters: 120 kV; 200–400 mA with automatic exposure control; 80 rows × 0.5-mm collimation; and helical pitch, 65 (pitch factor, 0.5). Each patient received an intravenous bolus injection of 135 mL contrast medium (Iomeron 350; Omnipaque, Eisai Co., Tokyo, Japan) from a power injector at 3.5 mL/s through a 20-gauge plastic IV catheter placed in an antecubital vein. The entire abdomen was scanned during the arterial phase (30–40 s after the introduction of contrast material). All images were reconstructed with a 0.5-mm effective thickness at 0.5-mm intervals, and slices were transferred to an image workstation (Ziostation2, Ziosoft Inc., Tokyo, Japan) to generate 3D images.

Diagnostic criteria for CTC

Colon and rectal walls appear as several layers on enhanced MDCT [16]. CTC criteria for T staging proposed by Filippone et al. [16] were as follows: T1/T2, smooth outer border of the thickened colorectal wall with a clear surrounding fat plane; T3, tumor with rounded or nodular advancing margin; and T4, obliteration of fat planes between colorectal tumor and adjacent organs.

Our newly developed criteria are as follows. The subserosal layer has rich adipose tissue which includes

marginal vessels (i.e., bordering vessels). Whereas the visceral peritoneum itself cannot be recognized on CT under normal conditions, the serosa exists between the bordering vessels and other organs, and physicians should be aware of its presence. The colon wall and rectal wall have a four-layered pattern. The most inner layer, a high-absorbance region, is a mucosal layer. The slight low-absorbance area of the second layer is a submucosal layer. The high-absorbance area of the third layer is the muscularis propria. The subserosal layer, where subserosal fat is not usually constant in thickness, ranges from the outer boundary of the muscular layer to the level of bordering vessels, and the layer of visceral peritoneum is a fat layer of the same thickness outside the bordering vessels. According to the new criteria, T3 and T4a are differentiated based on whether the tumor involves bordering vessels or not (Fig. 1). Representative cases for each T stage are provided below. Preoperative T staging using the new criteria was prospectively determined and compared with pathologic results.

Case 1

Figure 2 shows a 77-year-old male with T2 rectosigmoid colon cancer. MPR images show that the tumor did not reach the bordering vessels (arrow) and the outer border was smooth (a). Thus, preoperative T staging by CTC was T2. The macroscopic appearance of the tumor revealed irregular ulceration and clear marginal swelling (b). A resected specimen at the same level as captured by the MRP image revealed tumor invasion to the muscularis propria, but not to bordering vessels (arrow). The lesion was pathologically staged as T2 (c).

Case 2

Figure 3 shows a 72-year-old male with T3 sigmoid colon cancer. According to MPR images, the tumor reached the bordering vessels (arrow), but did not extend beyond them and had an irregular extramural layer (a). Thus, preoperative T staging by CTC was T3. Macroscopic appearance revealed the protuberant tumor with fold convergence (b). A resected specimen at the same level as captured by the MRP image revealed tumor invasion to bordering vessels (arrows) outside the muscularis propria. The lesion was pathologically staged as T3 (c).

Case 3

Figure 4 shows a 75-year-old male with T4a sigmoid colon cancer. According to MPR images, the tumor invaded beyond the bordering vessels (arrow) and had an irregular extramural layer (a). Thus, preoperative T staging by CTC was T4a. Macroscopic appearance revealed the subcircumferential tumor (53 mm in size) (b). A resected specimen at the same level as captured by the MRP image revealed tumor invasion beyond bordering vessels (arrows) and serosa. This lesion was pathologically staged as T4a (c).

Image analysis of CTC

Arterial phase contrast-enhanced transverse CT images were initially assessed, followed by a second review combining both arterial phase contrast-enhanced transverse images and MPR. CTC with MPR images was assessed preoperatively on the

Fig. 1 Diagnostic criteria for CTC. With respect to T staging based on the UICC TNM classification, bordering vessels distinguish T3 from T2 and T4. Tumors that do not involve bordering vessels and have a smooth outer border are considered T2, those with a rough border T3, and those that involve bordering vessels T4a
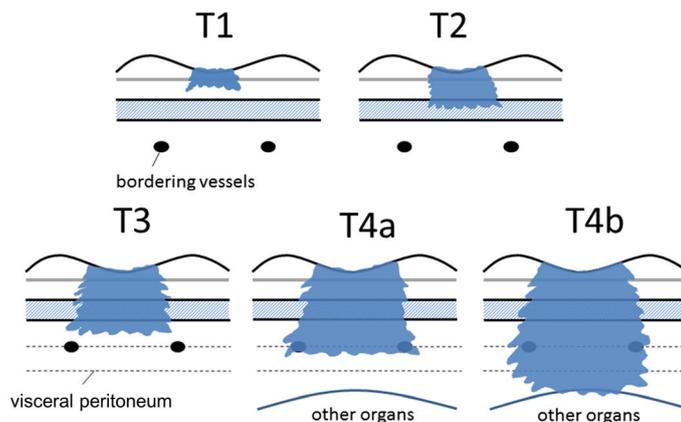
| Preoperative T staging	
T1	Tumors that localized within submucosal layer
T2	Tumors with smooth outer borders that do not involve bordering vessels
T3	Tumors with rough borders that do not involve bordering vessels
T4a	Tumors that involve bordering vessels

Fig. 2 A 77-year-old male with T2 rectosigmoid colon cancer. **a** MPR images revealed that the tumor does not involve bordering vessels (arrow) and has a smooth outer border. **b** The macroscopic appearance of the tumor revealed irregular ulceration and clear marginal swelling. **c** A resected specimen revealed tumor invasion to the muscularis propria, but not bordering vessels (arrow), with a pathological diagnosis of T2
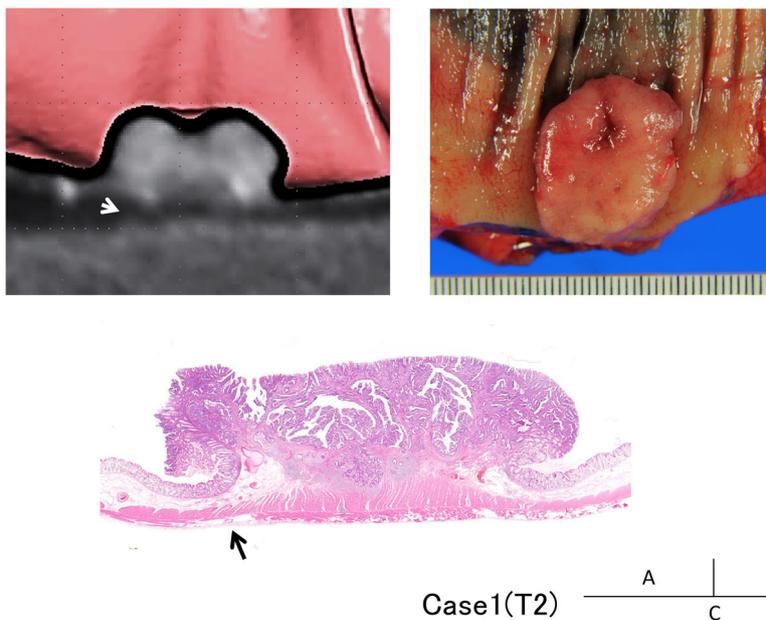
workstation independently by two experienced radiologists with at least 15 years of experience in abdominal CT interpretation and who were completely blinded to lesion size, macroscopic features, and stage of colorectal cancers. Differences in the assessment were resolved by consensus, which were only in a few cases. T staging was performed for CTC using MPR images generated from arterial and venous phase CT images. Depth of tumor invasion was assessed using the UICC TNM classification (8th edition) [1], as follows: pTis, carcinoma in situ: intraepithelial or invasion of lamina propria; pT1, tumor invades submucosa; pT2, tumor invades muscularis propria; pT3, tumor invades through the muscularis propria into pericolorectal tissues; and pT4, tumor penetrates to the surface of the visceral peritoneum (T4a) and tumor directly invades or is adherent to other organs or structures (T4b). Following this, the interpretation of the radiologists was confirmed preoperatively by at least four experienced surgeons at a conference in the colorectal surgery division of our hospital. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for T staging were evaluated.

Fig. 3 A 72-year-old male with T3 sigmoid colon cancer. **a** MPR images revealed that the tumor reached the bordering vessels (arrow), but did not extend beyond them, and had an irregular extramural layer. **b** Macroscopic appearance of the protuberant tumor with fold convergence. **c** A resected specimen revealed tumor invasion to bordering vessels (arrows) outside the muscularis propria, with a pathological diagnosis of T3
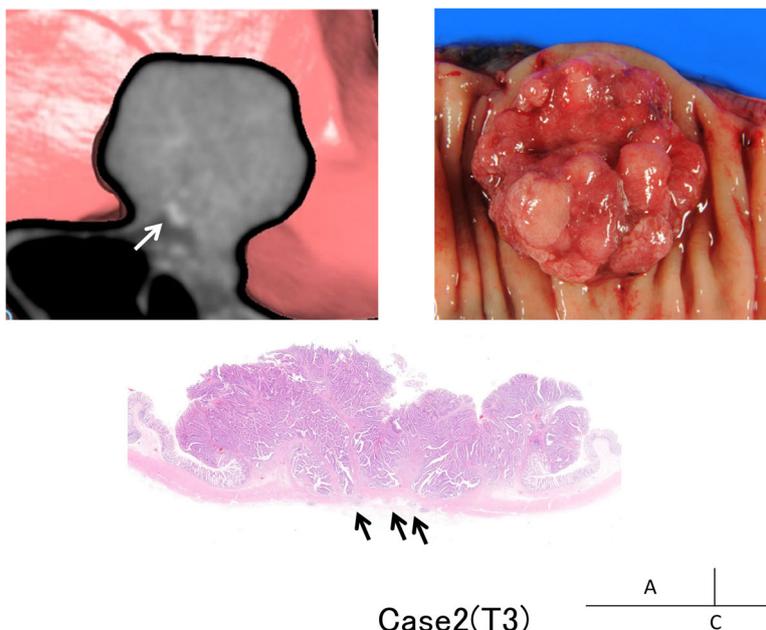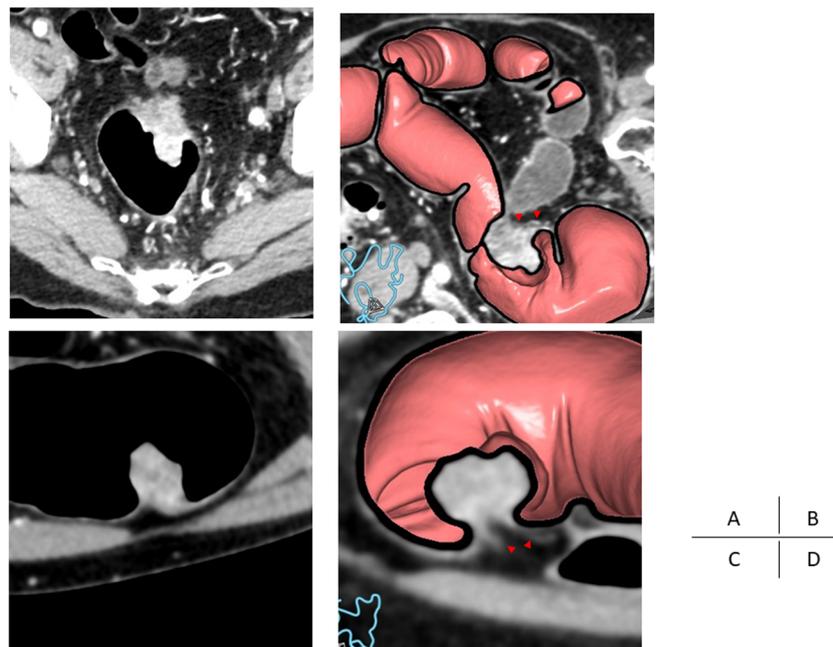
Fig. 4 A 75-year-old male with T4a sigmoid colon cancer. **a** MPR images revealed that the tumor invaded beyond the bordering vessels (arrow) and had an irregular extramural layer. **b** Macroscopic appearance of the subcircumferential tumor (53 mm in size). **c** A resected specimen revealed tumor invasion beyond bordering vessels (arrows) and serosa, resulting in a pathological diagnosis of T4a

Case3(T4a)
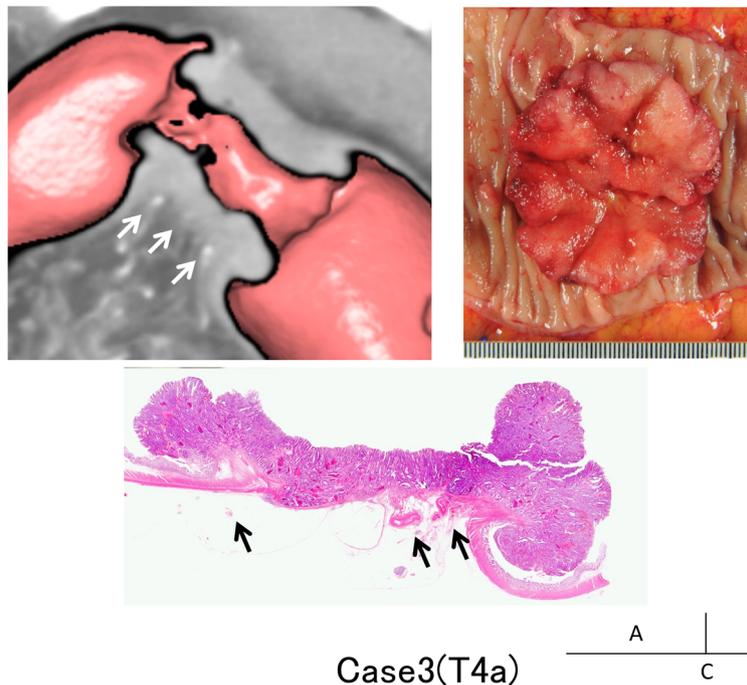
Results

Patient characteristics are as follows. There were slightly more male patients (55.8%) than female patients (44.2%). The mean age was 64.0 years. Tumor locations were right-side colon (30.2%), left-side colon (45.2%), and upper rectum (21.5%). Most tumors were histologically well and moderately differentiated adenocarcinomas (94.1%). At histopathological

Fig. 5 Two representative cases of colon cancers which were staged correctly by MPR images but not by normal CT images. **a, b** An 85-year-old male with pathological T3 rectosigmoid colon cancer. **a** Normal CT image showed that the tumor had an irregular extramural layer, which was considered T4a tumor. **b** MPR images showed that the tumor did not invade beyond the bordering vessels (arrow), which was considered T3 tumor. **c, d** A 65-year-old female with pathological T4a rectosigmoid colon cancer. **a** Normal CT image revealed that outer border of the small tumor was smooth, which was considered T2 tumor. **b** MPR images revealed that the tumor invaded beyond the bordering vessels (arrow), which was considered T4a tumor

	pT1, $n = 33$	pT2, $n = 30$	pT3, $n = 95$	pT4a, $n = 14$
Accuracy	91.3% (157/172)	76.7% (132/172)	81.4% (140/172)	97.1% (167/172)
Sensitivity	84.8% (28/33)	63.3% (19/30)	71.6% (68/95)	78.6% (11/14)
Specificity	92.8% (129/139)	79.6% (113/142)	93.5% (72/77)	98.7% (156/158)
PPV	73.7% (28/38)	39.6% (19/48)	93.2% (68/73)	84.6% (11/13)
NPV	96.3% (129/134)	91.1% (113/124)	72.7% (72/99)	98.1% (156/159)

Table 1 T staging accuracy of CTC

examination, 33 (19.2%) tumors were staged as pT1, 30 (17.4%) as pT2, 95 (55.2%) as pT3, and 14 (8%) as pT4a. All 172 tumors were identified on CTC with MPR images.

Comparison of normal CT images and MPR images of CTC

Figure 5 showed two representative cases indicating that MPR of CTC as a post-processing tool yields some added diagnostic value over normal CT images. Figure 5 (a and b) shows an 85-year-old male with pathological T3 rectosigmoid colon cancer which was staged correctly by CTC with MPR but overstaged by normal CT images. Figure 5 (c and d) shows a 65-year-old female with pathological T4a sigmoid colon cancer which was staged correctly by CTC with MPR but understaged by normal CT images.

Preoperative T staging

The accuracy of preoperative T staging for CTC is shown in Table 1. Sensitivity and specificity of T staging by CTC using the new criteria were 63% and 80% for T2 ($n = 30$); 72% and 94% for T3 ($n = 95$); and 79% and 99% for T4a ($n = 14$), respectively. Thus, the accuracy rates of T staging by CTC using the new criteria were 77% for T2; 81% for T3; and 97% for T4a.

It is important to know, for each group, how many patients were "under or over" staged by CT evaluation; in other words, how many T3 tumors on CTC were actually T3 at final pathologic examination as an example. Among 73 T3 tumors on CTC, 68 cases (93%) were actually pT3 whereas 3 were pT2 which were overstaged by CTC and 2 were pT4a which were understaged by CTC. And, among 13 T4a tumors on CTC, 11 cases (85%) were actually pT4a whereas 2 were pT3 which were overstaged by CTC. These data were shown as the results of PPV in Table 1. Thus, PPV for T3 was 93%.

It is also important to know how many "not T4a" tumors on CTC were actually "not T4a" at final pathologic examination. Among 159 "not T4a" tumors on CTC, 156 cases (98%) were actually "not pT4a." These data were shown as the results of NPV in Table 1. Thus, NPV in pathological T4a was 98%.

Discussion and conclusions

Preoperative T staging of colon cancer, in particular, for distinguishing T3 from T2 and T4, has been a challenge. In this study, we introduced newly developed diagnostic criteria for T staging of colon cancer by CTC with MPR. In the criteria, marginal vessels that are detectable by MDCT with MPR are referred to as "bordering vessels," and these bordering vessels play an important role in distinguishing T3 from T2 and T4. Specifically, tumors that do not involve bordering vessels and have a smooth outer border are considered T2, those with a rough border T3, and those that involve bordering vessels T4 (Fig. 1). Using these new criteria, we demonstrated that the accuracy of diagnosing T3 was 81.4% and that of T4a was 97.1%. These results suggest that the new criteria can diagnose T3 and "not T4a" in a precise manner. In previous reports, the overall accuracy of CTC for T staging ranged from 73 to 93%, and this may have been affected by patient inclusion criteria as well as the ratio of each T stage [16–19]. However, none of these previous reports were able to precisely distinguish T4a from T3, which is a point of novelty of our study.

Contrast-enhanced MPR images of gastric cancer can provide useful information about the gastric wall and depth of tumor invasion [20, 21]. In addition, virtual gastroscopy using MDCT images with air distention of the stomach can aid in T staging of gastric cancer [22, 23]. Compared to the gastric wall, the colon wall and rectal wall are much thinner and are thus considered more difficult to apply MDCT for T staging. However, recent advances in CT technology have prompted the consideration of its application to the staging of colorectal cancers. Filippone et al. reported that in T staging of colorectal cancer, the overall accuracy of MDCT was 73% when transverse images were evaluated alone, and 83% when they were evaluated in combination with MPR [16]. For rectal cancer, the overall accuracy of MDCT with MPR for T staging was reported to be 86% [24]. Compared with these reports, the accuracy rate in our study appears to be equivalent or better.

Recent developments in CTC with MPR and 3D images have made it possible to obtain highly accurate, thin slice images and optional images. Using the new image workstation, Zaiostation2, all images of CTC with MPR were reconstructed with a 1.0-mm effective thickness at 0.8-mm intervals, and slices were transferred to the workstation which

created the virtual line and images. This advanced workstation allows for MPR image analysis with a 0.5-mm slice thickness, whereas MRI can only analyze slice thicknesses up to 2 mm. MDCT with MPR can detect spatial relationships between tumors and bordering vessels, which are thought to comprise peripheral vessels, tumor-feeding vessels, and new blood vessels produced through tumor angiogenesis. Here, we proposed new diagnostic criteria for preoperative T staging by considering the involvement of bordering vessels: tumors that do not involve bordering vessels and have smooth outer borders are considered T2, those with rough borders T3, and those that do involve bordering vessels T4. Our results indicate that CTC using the new criteria had high diagnostic ability for staging T2, T3, and T4 tumors.

This study has two limitations worth noting. The evaluation was performed independently by two experienced radiologists specializing in the gastrointestinal tract who had experience with more than 500 CTC examination before the beginning of this study. Differences in assessment were resolved by consensus. Thus, we believe our results were not subjective but objective. However, this is somewhat limitation of our study. And the other limitation is that, while the new criteria are expected to distinguish T3 from T2 and T4, they must be tested by other groups and with a larger number of patients.

In conclusion, CTC with MPR using our new criteria for preoperative T staging is useful for distinguishing T3 from T2 and T4. These results highlight the utility of CTC with MPR as a diagnostic modality. CTC with MPR and the new criteria will need further refinement and validation before application to clinical settings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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