

Original Research Articles

Title: Preoperative T staging of advanced colorectal cancer by computed tomography colonography

Akira Komono¹⁾, Ryuji Kajitani¹⁾, Yoshiko Matsumoto¹⁾, Hideki Nagano¹⁾, Gumpei Yoshimatsu^{1), 2)}, Naoya Aisu¹⁾, Hiroshi Urakawa³⁾, Suguru Hasegawa¹⁾

- 1) Department of Gastroenterological Surgery, Fukuoka University Hospital
- 2) Department of Regenerative Medicine and Transplantation, Fukuoka University Hospital
- 3) Department of Diagnostic Radiology, Fukuoka University Hospital

Corresponding Author: Suguru Hasegawa, Department of Gastroenterological Surgery, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan. Telephone: +81-92-801-1011, Fax: +81-92-863-9759, E-mail address: shase@fukuoka-u.ac.jp, ORCID: 0000-0001-8044-4119

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Abstract

Purpose: Accurate preoperative T staging is important when determining the treatment strategy for locally advanced colorectal cancer. We have previously reported the usefulness of preoperative T staging based on the spatial relationship of tumors and “bordering vessels” by computed tomography colonography (CTC) with multiplanar reconstruction (MPR). The aims of this study were to evaluate the external validity of this

method and to determine whether there is a difference in the accuracy of preoperative T staging between the mesenteric and antimesenteric sides.

Methods: The study subjects were 110 patients with colorectal cancer who underwent preoperative CTC and surgical resection from June 2016 to March 2018. Patients who had received preoperative treatment were excluded. Preoperative T stage was determined by CTC based on the relationship between the tumor and the bordering vessels and compared with the pathological T stage. The influence of tumor location, namely, whether the tumor was on the antimesenteric or mesenteric side, on preoperative T staging was assessed in 78 patients with advanced colorectal cancer (excluding circumferential cases).

Results: Sensitivity, specificity, accuracy, positive predictive, and negative predictive values were respectively 65%, 91%, 83%, 76%, and 85% for T2 (n=34); 76%, 82%, 81%, 50%, and 94% for T3 (n=23); and 77%, 93%, 87%, 86%, and 88% for T4a disease (n=39). Overall right answer rate was 83.3% (15/18) for the mesenteric side and 65% (39/60) for the antimesenteric side (n=0.14).

Conclusion: Diagnostic criteria based on the bordering vessels seen on CTC images with MPR are useful for preoperative T staging of advanced colorectal cancer. However, the accuracy of preoperative T staging differs between the antimesenteric and mesenteric sides.

Keywords: preoperative T staging; CT colonography; multiplanar reconstruction; bordering vessels

Introduction

In recent years, the benefit of neoadjuvant chemotherapy has been investigated in patients with locally advanced colorectal cancer, and it has been suggested that accurate preoperative T staging has the potential to improve the treatment outcome [1] [2] [3]. The FOxTROT (UK), Prodige22-ECKINOXE (France), and NCT01918527 (Denmark, Norway, and Sweden) trials have investigated the benefits of preoperative chemotherapy in patients with high-risk T3 or T4 colon cancer. However, there is a need to reduce the number of false-positive cases in such trials to avoid overtreatment of patients who do not need antineoplastic therapy.

It is important to be able to distinguish T3 from T2 and T4 advanced colorectal cancer. In Japan, according to the Japanese Society for Cancer of the Colon and Rectum guidelines, the surgical treatment strategy for T2 and T3 disease differs in terms of the extent of lymph node dissection [4]. Moreover, the National Comprehensive Cancer Network guidelines point out that it is important to distinguish between T2 and T3 disease because neoadjuvant therapy is indicated for patients with cT3 or T4a rectal cancer. pT4a disease has a poor prognosis, and accurate clinical diagnosis of T4a disease may also be important [5]. The subgroup analysis of the recent JCOG0404 trial, which evaluated laparoscopic versus open complete mesocolic excision, identified T4 disease to be one of the factors contributing to the poor long-term outcome of laparoscopic surgery for stage II/III colorectal cancer, suggesting the need for careful consideration of whether to perform laparoscopic surgery in patients with T4 disease [6, 7].

The advent of multi-detector row CT (MDCT) has improved the quality of both axial and multiplanar reconstruction (MPR) images [8]. Filippone *et al.* reported that the overall accuracy of MDCT for T staging of colorectal cancer was 73% when transverse images

were evaluated alone and 83% when they were evaluated in combination with MPR [9]. For rectal cancer, the overall accuracy of T staging by MDCT with MPR was reported to be 86% [10]. However, it is still difficult to distinguish between T3 and T4a disease on CT, and T3 and T4a were analyzed together rather than separately in most of the previous research.

We have previously reported some useful new criteria for preoperative T staging by CTC with MPR. These criteria are based on the spatial relationship of tumors and the bordering vessels (marginal and subserosal) and are useful for distinguishing T3 from T2 or T4 disease [11] [12]. Although that research has made it easier to distinguish accurately between T3 and T4, the external validity of this method remains unclear. We have examined the value of preoperative T staging using these criteria in order to confirm their versatility. Using this method, the diagnosis depends on the bordering vessels in the subserosal adipose tissue, where there is a difference in fat thickness between the mesenteric and antimesenteric sides. Therefore, this study aimed to 1) evaluate the external validity of this method and 2) compare the accuracy of preoperative T staging according to whether the tumor is located on the mesenteric or antimesenteric side.

Patients and Methods

Patients

Patients who underwent preoperative CTC and surgical resection for colorectal adenocarcinoma at our hospital from June 2016 to March 2018 were enrolled in the study. Patients who received neoadjuvant radiation and/or neoadjuvant chemotherapy were excluded because of the inaccuracy of pathological T staging after neoadjuvant treatment. Since the new diagnostic criteria are used only for advanced colorectal cancer, patients with Tis and those who had undergone post-endoscopic resection were also excluded. All patients underwent conventional colonoscopy and CTC and provided written informed consent before these procedures. Surgical resection was performed within one month of CTC in all cases. T staging data were collected prospectively by CTC and analyzed retrospectively.

CT colonography protocol

The CTC procedures used have been described previously [13] [14]. All patients underwent MDCT with intravenous contrast medium immediately after conventional colonoscopy without stool tagging. Polyethylene glycol solution (Fusimi Pharma; Kagawa, Japan) was administered as bowel preparation before colonoscopy. An antiperistaltic agent (scopolamine butylbromide 20 mg) was administered intramuscularly before the CTC procedure. An enema tube was inserted into the rectum with the patient in the left lateral decubitus position. Automated carbon dioxide insufflation (PROTOCO2LTouch Colon Insufflator; Bracco Diagnostics Inc., Milan, Italy) was performed in all cases and the enema tube was left in the rectum during the examination.

CTC was performed using an 80x multidetector 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 a helical pitch of 65 (pitch factor, 0.5). Each patient received an intravenous 135-mL bolus injection of contrast medium (Iomeron 350, Eisai Co., Tokyo, Japan; Omnipaque, GE Healthcare Co., Tokyo, Japan) from a power injector at a rate of 3.5 mL/s through a 20-gauge plastic intravenous catheter placed in an antecubital vein. The entire abdomen was scanned during the arterial phase (30-40 s after introduction of contrast material). All images were reconstructed with a 0.5-mm effective thickness at 0.5-mm intervals. The slices were then transferred to a Ziostation2 workstation (Ziosoft Inc., Tokyo, Japan) to generate three-dimensional images.

Image analysis and diagnostic criteria

T staging was performed using CTC images with MPR obtained during the arterial and portal phases. Most diagnoses were made in the arterial phase while checking the bordering vessels. The deepest portion of the tumor was evaluated along a plane perpendicular to the longitudinal axis of the intestine using an MPR image to determine the T stage. Diagnoses based on the new criteria were made by a radiologist with 20 years of experience and one colorectal surgeon with 3 years of experience in abdominal CT. Both readers were blinded to the endoscopic diagnoses and other findings. Differences in diagnosis between the readers were resolved by discussion until consensus was reached.

The colorectal wall contains four layers: the mucosa, which is the innermost layer and has high absorbance; the submucosa, which is the second layer and has slightly low

absorbance; the muscularis propria, which is the third layer and has high absorbance; and the subserosa, which is rich in adipose tissue and includes marginal and straight bordering vessels. Although the serosal membrane cannot usually be detected on CT, it can be assumed to be just outside the bordering vessels.

According to the anatomic findings on CT, the depth of transmural invasion was categorized using the American Joint Committee on Cancer TNM classification [11]. The representative diagnostic criteria (Figs 1 and 2 [9]) are as follows: ctT1/T2, a thickened colorectal wall that has a smooth outer border with a clear surrounding fat plane (Fig 2a); ctT3, a tumor with a rounded or nodular advancing margin (Fig 2b); and ctT4a, obliteration of fat planes between the colorectal tumor and adjacent organs (Fig 2c)

Cases on the mesenteric side were defined as those in which the most invasive portion of the tumor was located on the side with the main vessel running through the mesentery and cases on the antimesenteric side were defined as those located on the other side (Fig 3). The two sides were compared in order to identify any difference in diagnostic ability.

Statistical Analysis

The sensitivity, specificity, accuracy, positive predictive, and negative predictive values for T staging by the new criteria were evaluated. We compared the accuracy for T staging of the infiltrating portion of the tumor located on the mesenteric side with that on the antimesenteric side in 78 patients with advanced colorectal cancer (excluding circumferential tumors). All statistical analyses were performed using the JMP15 software program (SAS Institute Japan Ltd., Tokyo, Japan). A p-value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Fukuoka University Hospital Institutional Review Board (approval number: U21-02-002) and conducted in accordance with the principles of the Declaration of Helsinki. The procedure of CTC was performed after obtaining patients' informed-consent.

Results

A total of 110 cases of colorectal cancer (110 lesions, located from the cecum to the upper part of the rectum) treated between June 2016 and March 2018 were included in the study. Patient characteristics are summarized in Table 1. Tumors were located in the right side of the colon in 34% of cases, the left side in 31%, and the upper part of the rectum in 35%. Most tumors (92%) were histologically well or moderately differentiated adenocarcinoma. On histopathological examination, 11 tumors (10%) were staged as pT1, 34 (31%) as pT2, 23 (21%) as pT3, 39 (35%) as pT4a, and 3 (2.7%) as pT4b. All 110 tumors could be identified on CTC images with MPR. The diagnostic accuracy of CTC for preoperative T staging is shown in Table 2. Accuracy, sensitivity, specificity, positive predictive, and negative predictive values for T staging by CTC were, respectively, 85.5%, 75.5%, 92.3%, 87.2%, and 84.5% for pT1-2 (n=45); 82.7%, 78.3%, 83.9%, 56.2%, and 93.6% for pT3 (n=23); and 87.3%, 76.9%, 93.0%, 85.7%, and 88.0% for pT4a (n=39) ($p < 0.0001$). Notably, the specificity for T4a (93.0%) and the negative predictive value for T3 (93.6%) were very high.

Table 3 shows the accuracy of preoperative T staging according to whether the tumor was on the mesenteric or antimesenteric side. The overall rate of right answers (right

answers / total number) was lower on the antimesenteric side than on the mesenteric side (65% [39/60] vs 83.3% [15/18]), although the difference was not statistically significant ($p=0.14$). On the antimesenteric side, the accuracy of T staging was 80.0% for pT1-2, 75% for pT3, and 76.7% for pT4a ($p<0.0001$); on the mesenteric side, the respective accuracy rates were 83.3%, 83.3%, and 100% ($p<0.0001$). For pT4a disease, the accuracy of preoperative T staging was lower on the antimesenteric side than on the mesenteric side. A representative case of underestimation of tumor depth is shown in Fig 4a. In this case, a pT4a lesion was misdiagnosed as cT2. On CT, the tumor had a smooth outer border and was diagnosed as cT2. The tumor was located on the antimesenteric side where there was no mesentery and the subserosal layer was thin (Fig 3, red star), and the diagnosis was difficult.

Discussion

Preoperative T staging of colon cancer is difficult because the intestinal tract runs in a different pattern to that of the rectum. In order to solve this problem, CTC is used to dilate and straighten the intestine and clarify how it runs. By using MPR images to construct a vertical slice aligned with the longitudinal plane of the intestine, it is possible to determine the T stage in the true axial plane of the tumor [15].

We have previously reported the usefulness of criteria based on the spatial relationship of tumors and bordering vessels for preoperative T staging of colorectal cancer by CTC with MPR [11] [12]. In the present study, we evaluated the external validity of these diagnostic criteria and found that they had high accuracy for distinguishing T3 from T2 and T4a disease, even at different institutions and in different patient cohorts. There have been various reports on T staging by CTC, with overall accuracy rates in the range of

73%-93% [9] [16, 17] [18] [19]. However, almost none of the previous studies could distinguish precisely between T3 and T4a disease, probably because of the difficulty recognizing the serosal membrane in a CT scan. An important feature of our diagnostic method is estimation of the thickness of the subserosal layer using the subserosal vessels as a landmark (Fig 2). In our reports, the accuracy was 82.7% for T3 and 87.3% for T4, suggesting that our diagnostic criteria can diagnose T3 and T4a disease in a precise manner.

In this study, the diagnostic accuracy for pT3 and pT4a disease was worse on the antimesenteric side than on the mesenteric side (75% and 76.7% vs 83.3% and 100%, respectively). In most cases, it is possible to distinguish the mesenteric side from the antimesenteric side by recognizing the main vessels (Fig3). As shown previously, the accuracy of our diagnostic method for distinguishing between cT2, T3, and T4a disease depends on the amount of change in the mesentery (adipose tissue) and bordering vessels around the tumor. On the antimesenteric side, where the subserosal adipose tissue is thin, a radiologic change in the subserosal layer is hard to detect. This is especially true in the area where the intestinal wall is not covered with mesenteric fat tissue (Fig 3, red star). Indeed, in this area, as shown in Fig 4a, even a relatively small (15-mm) tumor could invade the serosa (pT4a), but the diagnosis on CT may be underestimated as cT2. The thickness of the subserosal layer also depends on the location and amount of visceral fat. Liu et al. reported an increased probability of inaccurate T staging of colon cancer by CT in patients with less visceral adipose tissue [20].

This study has several limitations. First, the number of cases was small, especially on the mesenteric side. More cases are needed to ascertain the true significance of our

staging method. Second, the amount of experience in abdominal radiology needed to use these diagnostic criteria accurately is unclear. In this study, all radiologic diagnoses were made by the same two diagnosticians, one an experienced radiologist specializing in the gastrointestinal tract and the other a surgeon with experience in this diagnostic process [11]. It is unknown whether similar results could be obtained by other diagnosticians. However, despite these issues, we believe that the findings of this study will contribute to more accurate diagnosis of invasive colorectal cancer before treatment. In the future, the diagnostic accuracy of this method could be improved by introducing artificial intelligence technology and further improving the techniques used for image construction.

Conclusion

Diagnostic criteria using bordering vessels on CTC images with MPR are useful and versatile for pretreatment T staging of advanced colorectal cancer. Identification of the tumor location in relation to the mesentery is important for accurate preoperative T staging of colon cancer. Further research is needed to improve the accuracy of staging for tumors located on the antimesenteric side.

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Table 1. Patient characteristics

Sex, n (%)	Male	57 (52%)
	Female	53 (48%)
Age, years (range)		71 (32-89)
Body mass index (range)		21.8 (13-34)
Tumor size, mm (range)		36.6 (8-90)
Pathological T factor, n	T1b	11
	T2	34
	T3	23
	T4a	39
	T4b	3
Stage, n	I	38
	II	33
	III	30
	IV	9
Total		110

Table 2. Accuracy of T staging by CTC

	pT1-2 (n=45)	pT3 (n=23)	pT4a (n=39)	pT4b (n=3)
Accuracy	85.5% (94/110)	82.7% (91/110)	87.3% (96/110)	99% (109/110)
Sensitivity	75.5% (34/45)	78.3% (18/23)	76.9% (30/39)	100% (3/3)
Specificity	92.3% (60/65)	83.9% (73/87)	93.0% (66/71)	99% (106/107)
PPV	87.2% (34/39)	56.2% (18/32)	85.7% (30/35)	75% (3/4)
NPV	84.5% (60/71)	93.6% (73/78)	88.0% (66/75)	100% (106/106)

CTC, CT colonography; NPV, negative predictive value; PPV, positive predictive value

Table 3. Relationship between pathological T stage and CTC-diagnosed T stage

All cases (n=110)					
	ctT1-2	ctT3	ctT4a	ctT4b	Accuracy
pT1-2	34	9	2		0.855
pT3	2	18	3		0.827
pT4a	3	5	30	1	0.873
pT4b				3	0.99

Mesenteric side (n=18)					
	ctT1-2	ctT3	ctT4a	ctT4b	Accuracy
pT1-2	5	3			0.833
pT3		7			0.833
pT4a			3		1
pT4b					

Antimesenteric side (n=60)					
	ctT1-2	ctT3	ctT4a	ctT4b	Accuracy
pT1-2	15	6	2		0.8
pT3	1	8	3		0.75
pT4a	3	5	14	1	0.767
pT4b				2	0.987

CTC, CT colonography

Figure legends

Fig 1 Diagnostic criteria for CTC.

T2, T3, and T4a staging was determined by CTC based on the spatial relationship of tumors and bordering vessels.

CTC, CT colonography.

Fig 2 Representative cases for each T stage.

a: A case of pT2 cancer in the ascending colon. CTC imaging of the tumor with MPR revealed a tumor that was 13 mm in size and did not involve the bordering vessels (red arrow). It had a smooth outer border and was diagnosed as cT2.

b: A case of pT3 cancer in the sigmoid colon. CTC imaging with MPR revealed a tumor that was 40 mm in size and did not invade beyond the bordering vessels. It had an irregular outer border and was diagnosed as cT3.

c: A case of pT4a cancer in the sigmoid colon. CTC imaging with MPR revealed a tumor that was 40 mm in size. The tumor invaded beyond the bordering vessels and had an irregular outer border. It was diagnosed as cT4a. Sequential CTC images with MPR, from left to right, reveal that the bordering vessels are becoming gradually involved in the tumor. Red arrow: bordering vessels.

CTC, CT colonography; MPR, multiplanar reconstruction.

Fig 3 Definition of mesenteric side and antimesenteric side.

Cases on the mesenteric side were defined as those in which the most invasive portion of the tumor was located on the side with the main vessel running through the mesentery, and cases on the antimesenteric side were defined as those located on the other side.

Fig 4 Representative cases of pT4a disease diagnosed as cT2 and cT4a.

a: A case in which a pT4a cancer in the transverse colon was misdiagnosed as cT2. CTC imaging of the tumor with MPR revealed a tumor measuring 15 mm in size. The tumor was located in the antimesenteric side where there was no mesentery and the submucosal tissue was very thin. The tumor has a smooth outer border and was diagnosed as cT2. CTC, CT colonography.

Yellow line: the outer border of the tumor.

b: A case in which a pT4a cancer in the sigmoid colon was correctly diagnosed as cT4a. CTC imaging of the tumor with MPR revealed a tumor measuring 25 mm in size. The

tumor involved the bordering vessels (red arrow) and had an irregular outer border. It was diagnosed as cT4a.

CTC, CT colonography; MPR, multiplanar reconstruction.

Fig 5 A representative case of T4a cancer in the upper rectum.

a: CTC imaging of the tumor with MPR revealed a tumor measuring 40 mm in size.

b: According to the MPR images, the tumor was detected as the blue area. The tumor invaded beyond the virtual peritoneum but did not reach any other organs, and was diagnosed to be cT4a.

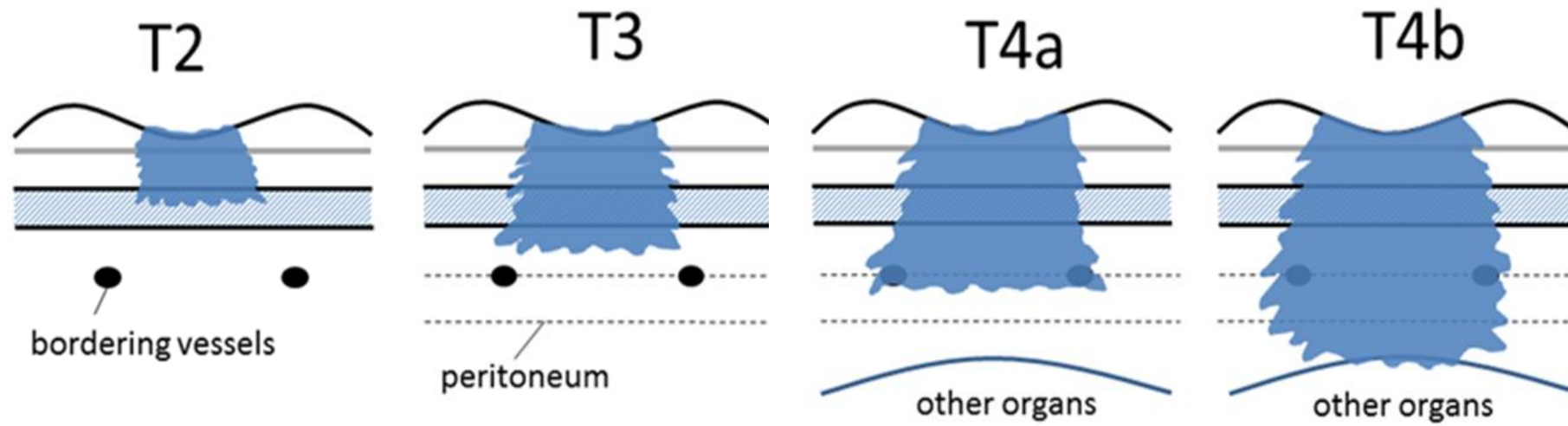
c, d: A resected specimen at the same level as that captured by the MRP image revealed tumor invasion to the peritoneum. The lesion was pathologically staged as pT4a.

The thickness of the adipose tissue on the mesenteric side (Fig 5d; blue arrow) is different from that on the antimesenteric side (Fig 5d; red arrow).

Red line: bordering vessels. T: tumor. Yellow dotted line: virtual peritoneum.

CTC, CT colonography; MPR, multiplanar reconstruction.

Fig 1



Preoperative T staging	
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

Fig2

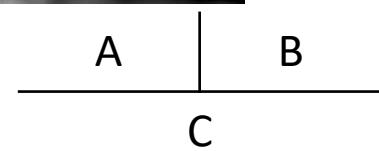
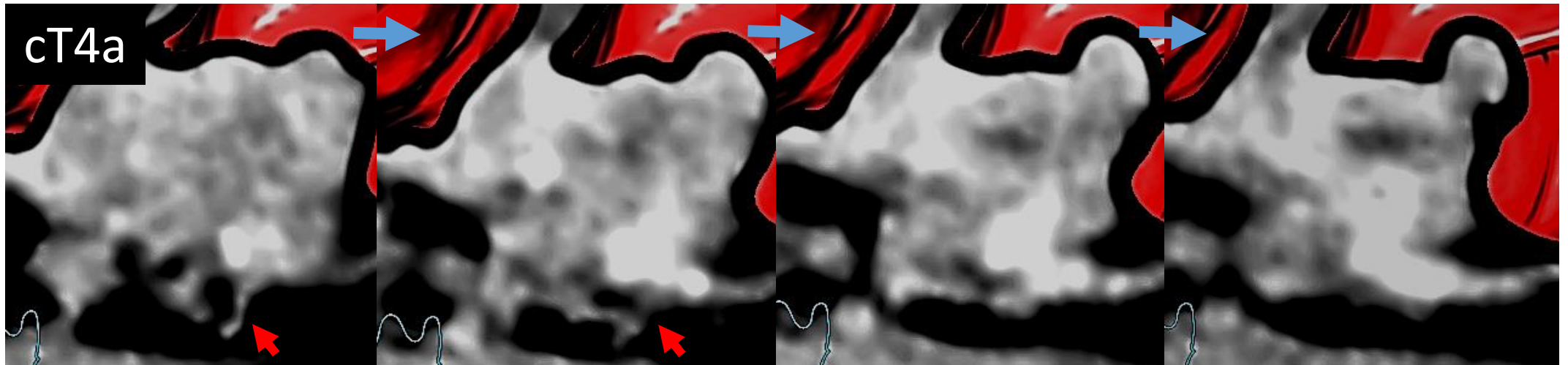
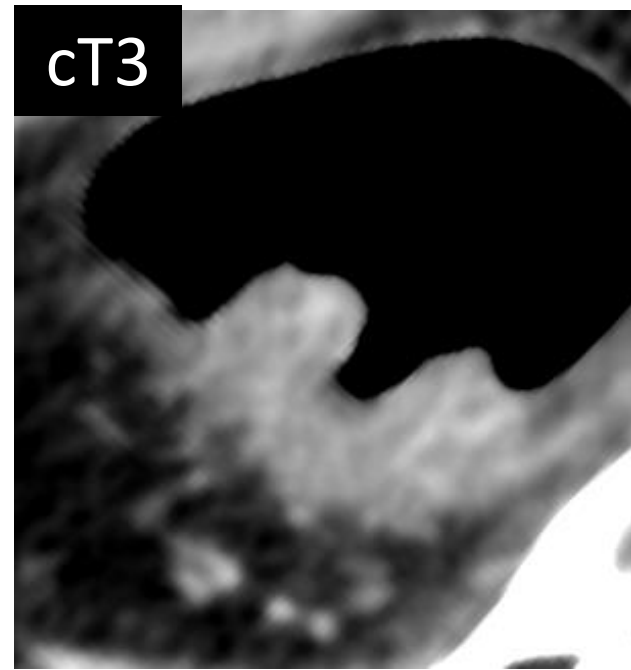
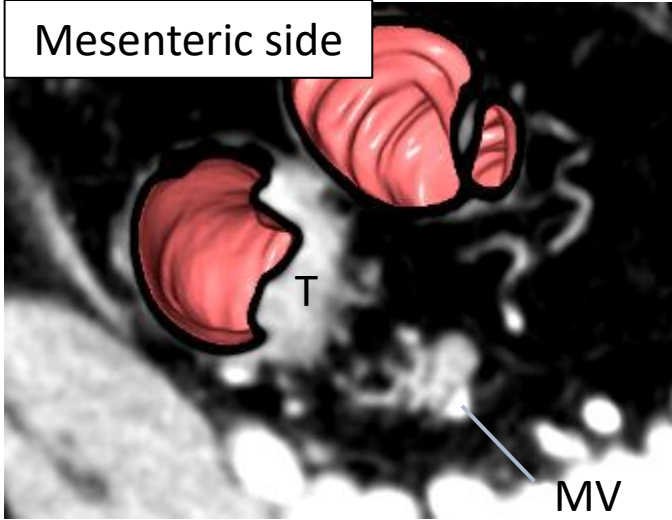
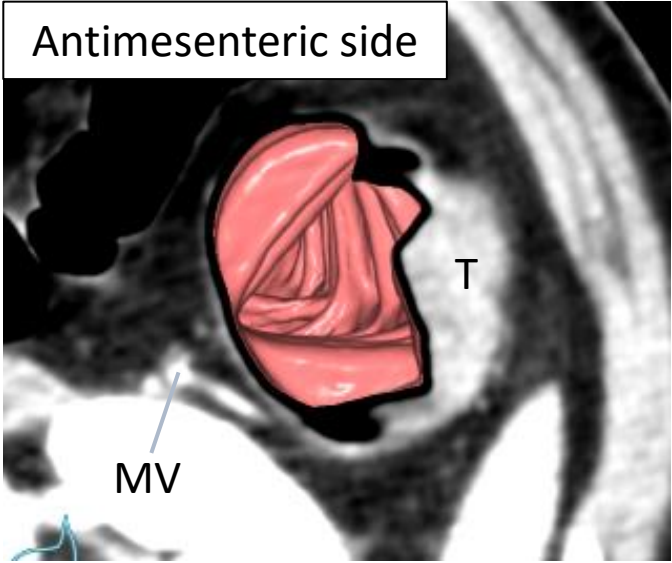
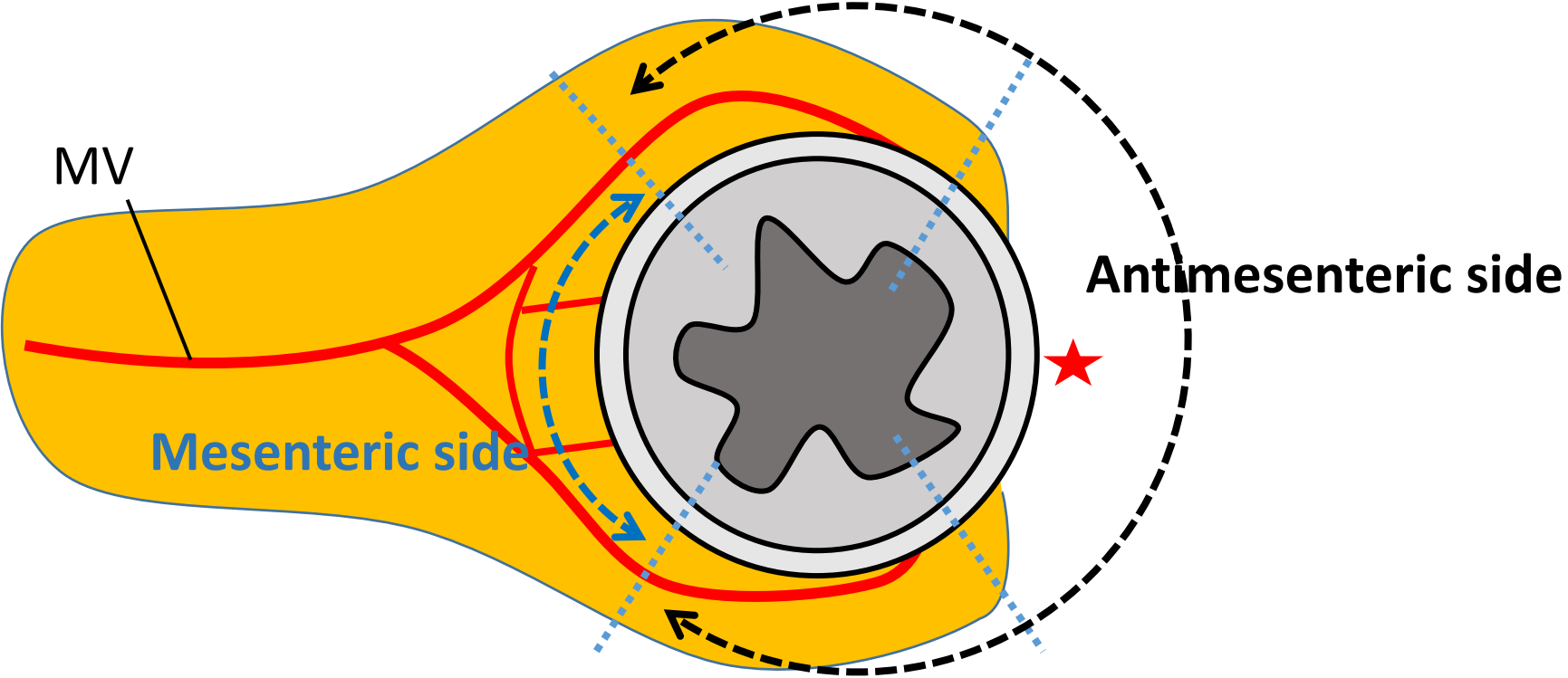


Fig3



T: tumor
MV: Main Vessel

Fig4-a

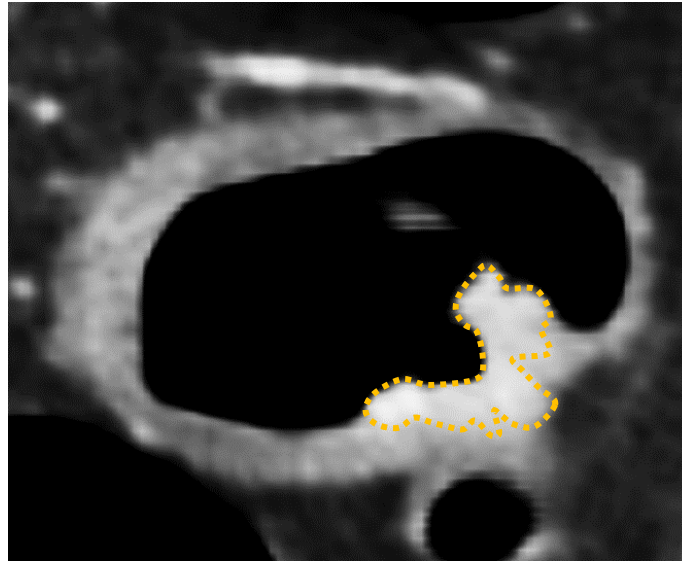
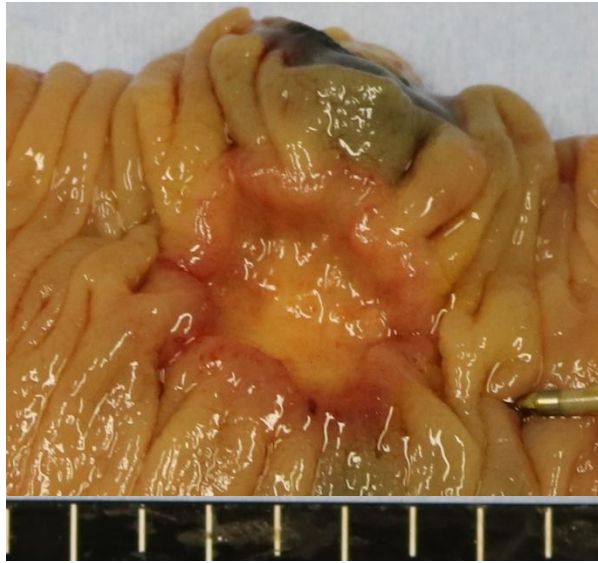
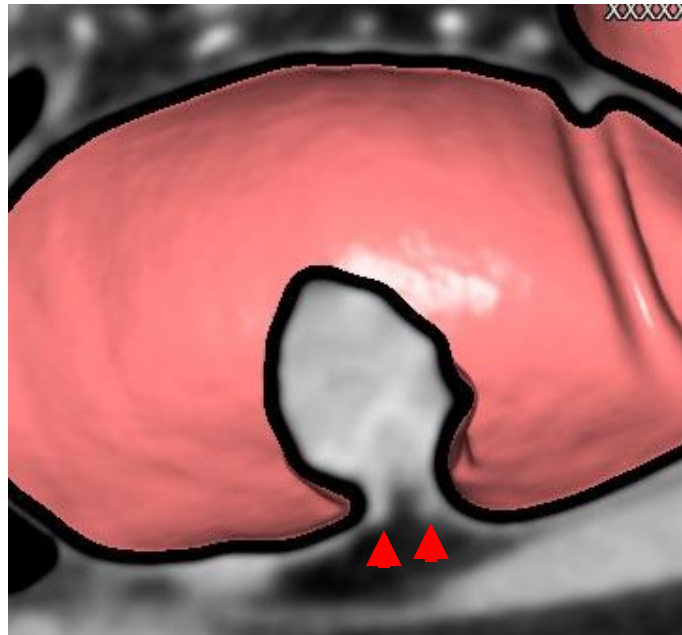


Fig4-b



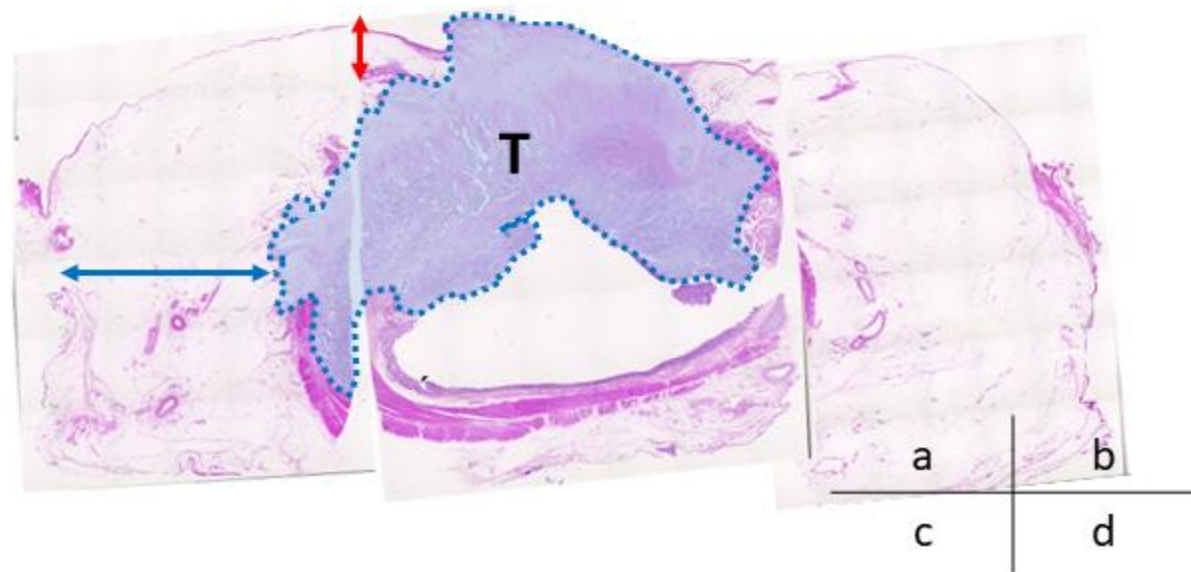
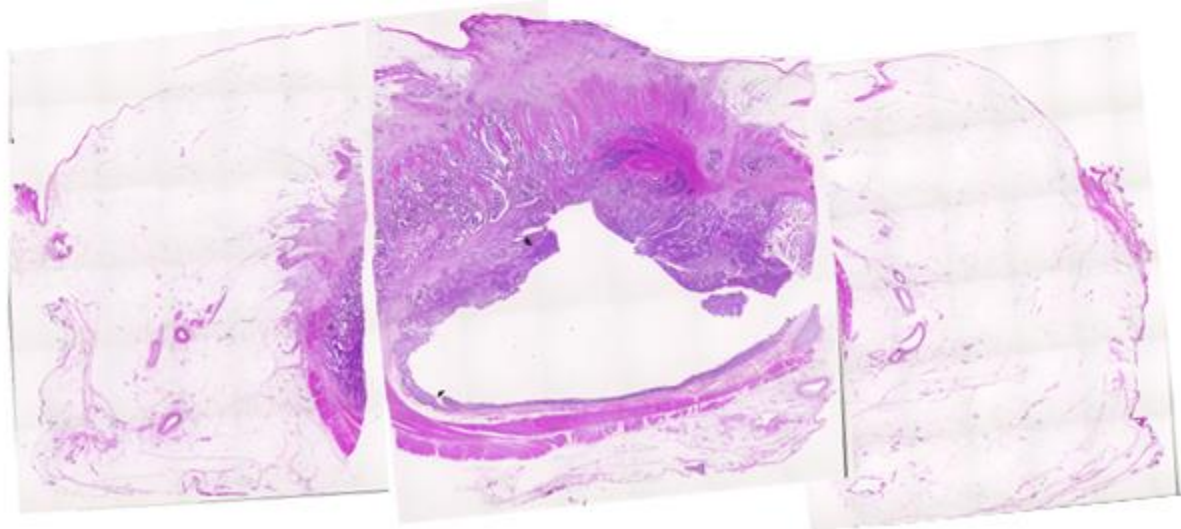
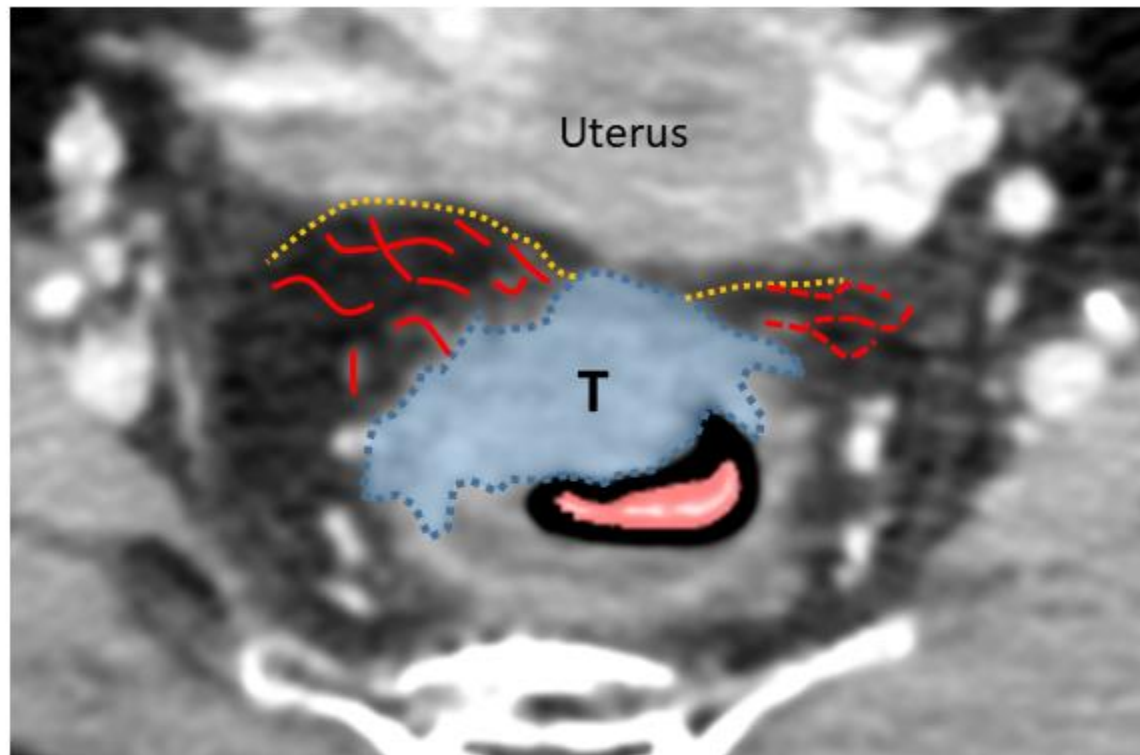
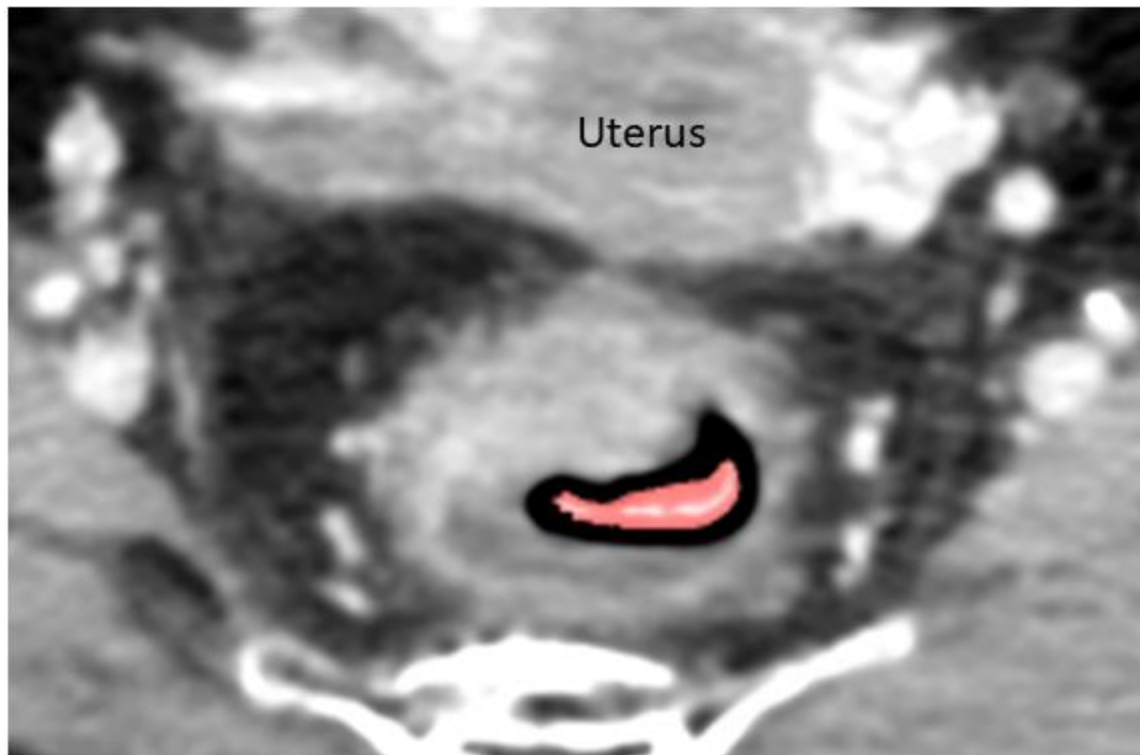


Fig5