Original research

Correlation between CT morphologic appearance and histologic findings in colorectal liver metastasis after preoperative chemotherapy

Kazuyuki Ishida,[1] Akio Tamura,[2] Kenichi Kato,[2] Noriyuki Uesugi,[1] Mitsumasa Osakabe,[1] Makoto Eizuka,[1] Yasushi Hasegawa,[3] Hiroyuki Nitta,[3] Koki Otsuka,[3] Akira Sasaki,[3] Shigeru Ehara[2] and Tamotsu Sugai[1]

[1]Department of Molecular Diagnostic Pathology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, JAPAN

[2]Department of Radiology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, JAPAN

[3]Department of Surgery, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, JAPAN

*Corresponding author:

Kazuyuki Ishida, M.D., Ph.D.

Department of Molecular Diagnostic Pathology, Iwate Medical University, 19-1

Uchimaru, Morioka, Iwate 020-8505, JAPAN

TEL: +81-19-651-5111 (ext. 3695)

Facsimile: +81-19-629-1436

E-mail address: ishidaka@iwate-med.ac.jp

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Abstract

Purpose: Radiological evaluation of the efficacy of preoperative chemotherapy for colorectal liver metastasis (CRLM) is the most important tool for determining treatment strategies. The aim of this study was to identify a correlation between morphologic appearance on computed tomography (CT) and histologic findings of CRLM after preoperative chemotherapy.

Methods: We examined 47 patients who had undergone a first hepatic resection for CRLM after preoperative chemotherapy and had received contrast-enhanced CT scans. We assessed the morphologic appearance of the overall attenuation based on metastases changing from heterogeneous to mixed and homogenous lesions, the tumor–liver interface and the peripheral rim enhancement on CT. Histologic parameters included usual necrosis (UN), infarct-like necrosis (ILN), three-zonal change, dangerous halo, mucous lake, shape of ILN, dominant type of necrosis and presence of viable tumor cells. The relationship between morphologic appearance and histologic findings was evaluated.

Results: CT overall attenuation revealed that UN predominance was more common in the heterogeneous group than in the mixed and homogeneous groups ($P = 0.011$). The frequency of ILN increased sequentially from ill-defined to variable and sharp at the tumor-liver interface ($P = 0.038$), and the frequency of UN decreased sequentially from present to partially resolved and completely resolved in the peripheral rim enhancement ($P = 0.023$).

The histologic presence of viable tumor cells was closely associated with the tumor-liver interface ($P = 0.0003$) and the peripheral rim enhancement ($P = 0.004$).

Conclusions: CT morphologic appearance of CRLM after preoperative chemotherapy is correlated with histologic findings regarding necrosis.

Keywords:

Colorectal Carcinoma; Metastasis; Liver Neoplasms; Computed Tomography, X-ray; Comparative Histology

Colorectal liver metastasis (CRLM) is the most common complication of colorectal cancer [1, 2], and radical surgical resection is the only treatment that can provide prolonged survival or even a cure [3–5]. However, most cases of CRLM are unresectable at the time of diagnosis [6]. Preoperative chemotherapy provides the potential to shrink initially unresectable lesions to make surgery possible [7–9]. Radiological evaluation of the efficacy of preoperative chemotherapy for CRLM is the most important tool to decide treatment strategies, including adaptation of the surgery.

The Response Evaluation Criteria in Solid Tumors (RECIST) have been used radiologically to evaluate the effect of preoperative chemotherapy [8, 10, 11]. However, RECIST criteria, which were the conventional tumor size-based radiologic criteria, may not be sufficient to assess the response to chemotherapy, especially in patients treated with a regimen including bevacizumab, a monoclonal humanized antibody directed against vascular endothelial growth factor [12–14]. Recently, it was reported that morphologic criteria observed on contrast-enhanced computed tomography (CT) scans were significantly correlated with pathologic response and overall survival in patients treated with preoperative chemotherapy for CRLM [15], and these findings were later validated [16-18]. Morphologic criteria were assigned to three groups, reflecting the appearance of three radiological features: overall attenuation, tumor-liver interface, and peripheral rim enhancement. However, relevant

histologic findings have not yet been correlated with morphologic appearance on contrast-enhanced CT scans.

Recent studies have shown that the histologic tumor response to preoperative chemotherapy for CRLM is associated with postoperative disease-free and overall survival [19–21]. Patients who responded well to preoperative chemotherapy for CRLM, with less than 50% of the cancer cells remaining in the tumor, had significantly better outcomes compared with patients who responded poorly, with more than 50% of the cancers cells remaining in the tumor [19–21]. In addition, detailed histologic findings for evaluating the effectiveness of preoperative chemotherapy and differences associated with various treatment regimens have been proposed [22–24]. Histologic findings of infarct-like necrosis (ILN) and three-zonal changes were more frequent in patients with CRLM who underwent preoperative chemotherapy than in patients who did not [22, 23, 25]. The incidence of usual necrosis (UN) was significantly decreased with preoperative chemotherapy regimens that included bevacizumab [22]. In addition, patients with ILN had superior disease-free survival compared with those with UN among those receiving preoperative chemotherapy [23]. Dangerous halo was regarded as a regrowth finding of CRLM when chemotherapy was interrupted, and was deemed to require adaptation of the surgical technique to decrease the risk of local recurrence [19, 26]. Acellular mucin was regarded as a form of tumor response to preoperative chemotherapy [19]. Accordingly, histologic findings of CRLM after preoperative

chemotherapy have elucidated the effects of preoperative chemotherapy and could divide patients with CRLM with medication into a well-responded group or an ill-responded group. Hence, if the CT findings correlate with histologic findings that predict a good responder or a poor responder, radiologists could determine the probability of a good treatment response based on the likely histologic findings.

The purpose of this study was to determine whether a correlation existed between morphologic appearance on CT and histologic findings of CRLM after preoperative chemotherapy.

Materials and Methods

We examined 47 patients with colorectal carcinoma from 2008 to 2013 who had undergone a first hepatic resection for CRLM after preoperative chemotherapy. Patients were eligible if they had the following: (i) preoperative contrast-enhanced CT scan performed within 2 months before surgical resection, (ii) CRLM detectable on preoperative CT, and (iii) diagnosis of CRLM confirmed by histopathologic examination. Among the preoperative chemotherapeutic regimens used were 5-FU, 5-FU with leucovorin and oxaliplatin (FOLFOX), 5-FU with leucovorin and irinotecan (FOLFIRI), and FOLFOX or FOLFIRI with bevacizumab.

All CT examinations were performed with either a 16-slice or 64-slice multi-detector CT scanners (Light Speed VCT 64 Slice CT, GE Healthcare, Wauwatosa, WI, USA; Toshiba Aquilion 16 or 64, Toshiba Medical Systems, Tokyo, Japan). Contrast-enhanced CT of the liver was performed as part of the routine liver/abdomen CT protocol with intravenous application of non-ionic contrast medium containing an iodine concentration of 300 mg/mL (Iopamiron 300, BayerSchering Healthcare, Leverkusen, Germany; Omnipaque 300, Daiichi Sankyo, Tokyo, Japan) at a dose of 2 ml/ kg body weight injected with a power injector (Nemoto DUAL SHOT Type D). The scan delay for arterial phase imaging was determined with an automatic bolus-tracking program (Toshiba, Tokyo, Japan). Scanning for the arterial and portal venous phases was started automatically at 20 and 60 s, respectively, after the trigger threshold (100 HU) was reached at the level immediately above the celiac trunk. Pre-contrast images were also obtained in all patients; however, arterial phase images were not evaluated in this study. Routine dataset reconstructions at 3-mm section thickness and 3-mm reconstruction increments were used for image assessment. Morphologic appearance on contrast-enhanced CT scans for CRLM after preoperative chemotherapy was assessed by two radiologists (with 8 and 20 years of experience with body CT, respectively) blinded to the pathologic results, patient treatments, and outcomes. Discrepancies between radiologists were resolved by consensus review. In patients with multiple metastases, the lesion with the greatest diameter was examined. Three morphologic features of CRLM were evaluated,

according to the following previously described classifications: overall attenuation was classified as heterogeneous, mixed, or homogeneous and hypoattenuating; tumor-liver interface was classified as ill-defined, variable, or sharp; and peripheral rim enhancement was classified as present; if initially present, partially resolved; and, if initially present, completely resolved [15]. Representative CT images of the morphological appearance of CRLM are shown in Figure 1.

Hepatectomy specimens of CRLM after chemotherapy, which were originally prepared from formalin-fixed, paraffin-embedded tissue, were stained with hematoxylin and eosin according to our routine hospital process. In patients with multiple metastases the lesion with the greatest diameter was examined, which fit a radiological target lesion. Samples were systematically taken for histology from the whole section. Slides were evaluated by two pathologists (with 14 and 20 years of experience in pathology, respectively) blinded to the subjects' clinical data. Discrepancies between pathologists were resolved by consensus review.

The following histologic findings were evaluated: usual necrosis (UN), infarct-like necrosis (ILN), three-zonal change, dangerous halo and mucous lake (Figure 2). UN, which is traditionally seen in colorectal adenocarcinomas, was defined as containing nuclear debris in a patchy distribution, with the necrosis admixed and bordered by viable cells. In contrast, ILN, which is more common in patients with CRLM exposed to medications, was defined as being

composed of large confluent areas of eosinophilic cytoplasmic remnants located centrally within a lesion with absent or minimal admixed nuclear debris [22]. UN and ILN were defined as positive when they occupied more than 5% of the tumor area. Three-zonal change, which is frequently observed in patients treated with preoperative chemotherapy, such as a central zone of necrosis, a middle zone of fibrosis, and an outer zone of residual tumor, was noted [25]. A dangerous halo showed that viable tumor cells appeared to infiltrate the surrounding liver parenchyma without a fibroinflammatory reaction [26], and was defined as positive when it occupied more than 10% of all circumferences. A mucous lake, formed of extracellular mucin, was defined as positive when it occupied more than 30% of the tumor area. Necrotic characteristics, such as the shape of the ILN and the dominant type of necrosis, were also evaluated. The appearance of ILN was classified into central ILN, speckled ILN, or neither. Central ILN was present in the center of the tumor, and tumor cells surrounded the circumference with or without intervening fibrosis [27]. Speckled ILN produced a number of lumps in the tumor with fibrosis (Figure 3). In each case, we determined the dominant type of necrosis; that is, whether UN or ILN was more prominent. The presence of viable tumor cells was assessed semiquantitatively as a percentage relative to the total tumor area [20, 21, 28]. UN was considered to denote an area of viable tumor cells, and ILN an area of fibrosis [22, 23].

The analysis was performed with Microsoft Excel 2013 version (Microsoft, Redmond, WA, USA). Statistical significance was evaluated with a χ^2-test, and $P < 0.05$ was considered significant.

Results

The median age of the study population was 66 years (range 41-82), and there were 31 men and 16 women. Nine patients had a synchronous liver metastasis with colon cancer, and 38 patients had metachronous metastases. The median number of metastases was two (range, 1 to 11), and the median diameter of the largest metastasis was 23.5 mm (range, 7 to 155 mm). Several different protocols of preoperative chemotherapy were used: 12 patients received 5-FU only (5-FU group); 9 patients received FOLFOX or FOLFIRI (FOLFOX or FOLFIRI group); and 26 patients received FOLFOX or FOLFIRI with bevacizumab (FOLFOX or FOLFIRI with bevacizumab group). The patient clinicopathological characteristics by type of preoperative chemotherapy are summarized in Table 1.

We evaluated the 3 types of morphologic appearances on contrast-enhanced CT scans for CRLM after preoperative chemotherapy. For overall attenuation, the heterogeneous group had 16 patients (34.0%); the mixed group had 13 patients (27.7%); and the homogeneous and hypoattenuating group had 18 patients (38.3%). For tumor-liver interface, the ill-defined group had 17 patients (36.2%); the variable group had 18 patients (38.3%); and the sharp

group had 12 patients (25.5%). For peripheral rim enhancement, the present group had 16 patients (34.0%); if initially present, the partially resolved group had 18 patients (38.3%); if initially present, the completely resolved group had 13 patients (27.7%).

Correlations between CT overall attenuation and histologic findings are shown in Table 2. No mucous lakes were observed in the heterogeneous group; they were found only in the mixed and homogeneous groups (0/16 [0%], 5/13 [38.5%], 5/18 [27.8%], respectively) (P = 0.029). Examination of the dominant type of necrosis revealed that as overall attenuation changed sequentially from the heterogeneous group to the mixed group to the homogeneous group, UN predominance decreased (12/16 [75.0%], 5/13 [38.5%], 4/18 [22.2%], respectively), and ILN predominance increased from the heterogeneous group to the mixed and homogeneous groups (4/16 [25.0%], 8/13 [61.5%], and 11/18 [61.1%], respectively) (P = 0.011). The other histologic findings, including the presence of viable tumor cells, did not show significant differences among the three groups.

As shown in Table 3, CT examination of the tumor–liver interface revealed that the frequency of ILN progressively increased from the ill-defined group, to the variable group, to the sharp group (6/17 [35.3%], 10/18 [55.6%], 10/12 [83.3%], respectively) (P = 0.038). The histologic presence of viable tumor cells was closely associated with the tumor-liver interface (P = 0.0003). There were no cases with 0-10% viable tumor cells in the ill-defined or variable groups, but 41.7% (5/12) of the cases in the sharp group showed 0-10% viable tumor cells.

Cases with 11-50% viable tumor cells were more common in the variable group (10/18 [55.6%]) than in the ill-defined group and the sharp group (4/17 [23.5%] and 2/12 [16.7%], respectively). Cases with 51-100% viable tumor cells were more common in the ill-defined group (13/17 [76.5%]) than in the variable and sharp groups (8/18 [44.4%] and 5/12 [41.7%], respectively).

The correlation between CT peripheral rim enhancement and histologic findings is shown in Table 4. UN was significantly associated with peripheral rim enhancement, and its frequency decreased, sequentially, from the present to the partially resolved and completely resolved groups (16/16 [100%], 15/18 [83.3%], 8/13 [61.5%], respectively) (P = 0.023). The histologic presence of viable tumor cells was significantly associated with peripheral rim enhancement (P = 0.004). Here, there was a major difference between the completely resolved group, and the other two groups, with cases with 0-10% viable tumor cells being more common in the completely resolved group (5/13 [38.5%]) than in the present and partially resolved groups (0/16 [0%] and 0/18 [0%], respectively), and cases with 51-100% viable tumor cells being more common in the present and partially resolved groups (10/16 [62.5%] and 12/18 [66.7%], respectively) than in the completely resolved group (4/13 [30.8%]).

Discussion

Improvements in the efficacy of chemotherapy have not only improved patient survival in a palliative condition but have also presented an opportunity for cure to patients with previously unresectable disease by enabling liver surgery after tumor downstaging [8, 29]. Radiological evaluation of the effects of preoperative chemotherapy for CRLM is the most important method for deciding treatment strategies, including adaptation of surgery. However, RECIST criteria, which are the conventional tumor size-based radiologic criteria, may be inadequate to assess the response to chemotherapy with a regimen including bevacizumab [12–14]. Meanwhile, Chun et al. reported morphologic criteria based on morphologic changes observed on CT in patients with CRLM undergoing preoperative bevacizumab-containing chemotherapy [15]. Morphologic criteria were assigned to three groups, reflecting the morphologic appearance of three radiological features: overall attenuation, tumor-liver interface, and peripheral rim enhancement. However, relevant histologic findings have not been correlated with CT morphologic appearance. Our study further clarified the following: overall CT attenuation of CRLM with preoperative chemotherapy correlated with the dominant type of necrosis and mucous lake formation. The tumor-liver interface was associated with ILN, and especially with the residual viable tumor cells. Peripheral rim enhancement was correlated with UN and the quantity of viable tumor cells, particularly in patients with CRLM assessed with less than 10% viable tumor cells after preoperative

chemotherapy. This is the first report presenting a correlation between morphologic appearance and characteristic histologic findings in CRLM with preoperative chemotherapy.

In this study, the CT morphologic appearance in CRLM was associated with histologic findings regarding necrosis, in particular, when we classified necrosis into UN and ILN. Primary colorectal cancer has abundant necrosis, generally, and necrosis is more frequent in a metastasis than in a primary tumor. Therefore, the histologic evaluation of necrosis in CRLM with preoperative chemotherapy has not been well established, and the results have been conflicting. Some investigators reported that the necrosis was seen more in patients who underwent surgery alone and in those who responded poorly to chemotherapy [19, 30], and others reported that the presence of necrosis was a finding of response to chemotherapy [25]. Recent studies showed that necrosis in CRLMs should be histologically classified into UN, which appears more frequently in all CRLM patients, and ILN, which has a significant appearance in preoperative chemotherapy groups [22, 23]. Therefore, we presumed the possibility that radiological assessment to evaluate CRLMs after preoperative chemotherapy qualitatively, especially by CT morphologic appearance, correlated with the characteristic necrosis. Our present study revealed that histologic characteristic necrosis was closely correlated with three morphologic appearances: the histologic dominant type of necrosis was associated with overall attenuation; the histologic presence of ILN was associated with the tumor-liver interface; and the presence of UN was associated with

peripheral rim enhancement. In addition, the histologic quantity of residual tumor cells was closely associated with the tumor-liver interface and peripheral rim enhancement, when UN was considered to denote an area of viable tumor cells, and ILN an area of fibrosis. Therefore, we should distinguish between UN and ILN in the radiological and pathological evaluation of the response to preoperative chemotherapy for CRLM.

We evaluated the histologic findings of necrotic characteristics in CRLM after preoperative chemotherapy, such as the shape of ILN and the dominant type of necrosis. With regard to the shape of ILN, central ILN was mentioned in a figure of a previous report [27]. In addition, we classified ILN into central and speckled ILN. As there were 21 cases without ILN, there was no significant difference in the shape of ILN between each CT morphologic appearance and the histologic findings. However, the frequency of central ILN tended to increase, and that of speckled ILN to decrease, from the heterogeneous to the mixed group in overall attenuation. Necrotic characteristics, not only the dominant type of necrosis but also the shape of ILN, may be related with an overall attenuation in CRLM after preoperative chemotherapy. Meanwhile, it was reported that ILN in CRLM after preoperative chemotherapy was associated with patients treated with a regimen including bevacizumab [22, 27]. Our study showed that the frequency of central and speckled ILN was 29.8% (14/47) and 23.4% (11/47), respectively, in the all preoperative chemotherapy group, whereas it was 42.3% (11/26) and 23.1% (6/26), respectively, in the FOLFOX or FOLFIRI with bevacizumab

group. In a comparison between CT morphologic appearance and histologic findings, the FOLFOX or FOLFIRI with bevacizumab group showed a similar tendency to the all preoperative chemotherapy group (data not shown).

Chun et al. found that assessment of the morphologic response to preoperative chemotherapy had high reproducibility with good interobserver agreement [15]. Optimal morphologic response was assigned to three groups in combinations of the three morphologic appearances. However, we revealed that three morphologic appearances on CRLM CT scans were also correlated with characteristic histologic findings (Figure 4). On the basis of these results, we propose that the diagnostic clue to evaluate morphologic response to preoperative chemotherapy for CRLM is as follows: first, the reactivity to the chemotherapy regimen (in other words, the change from UN to ILN) was evaluated by the overall attenuation. Second, the quantity of residual viable tumor cells was assessed by the tumor-liver interface and peripheral rim enhancement. Notably, as the tumor-liver interface from the ill-defined, variable, and sharp groups was especially associated with the sequential decrease of residual tumor cells, the tumor-liver interface was a good parameter when CRLM patients after preoperative chemotherapy were divided into well-responded or ill-responded groups. In addition, peripheral rim enhancement was useful, particularly to assess whether less than 10% viable tumor cells were present in CRLM patients after preoperative chemotherapy.

The limitations of this study include the retrospective analysis of data and the selected population at a single institution, which would have unavoidably introduced selection bias. We suggest that results from a larger cohort of patients will be needed to have an impact on the current treatment strategies for CRLM. Second, the patients in this study were treated with fluorouracil-based chemotherapy including oxaliplatin or irinotecan with or without bevacizumab, but other biologic agents, such as cetuximab, which produce high response rates and improve resectability, were not included [31]. Third, some of the morphologic patterns on CT findings were subjective, and interobserver variation existed. In this study, discrepancies between radiologists were resolved by consensus review. Recently, Ng et al. reported that CT texture features of primary colorectal cancer were related to the 5-year overall survival rate [32]. CT texture analysis could reduce the effect of photon noise while enhancing biologic heterogeneity. The residual tumor cells in CRLM after preoperative chemotherapy might be quantified objectively by CT texture analysis.

In conclusion, the results of the current study indicate that the morphologic appearance of CRLM after preoperative chemotherapy on contrast-enhanced CT scans is correlated with characteristic histologic findings and the histologic tumor response.

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Figure Captions

Fig. 1. Representative morphological appearance of colorectal liver metastases on contrast-enhanced CT after preoperative chemotherapy. (a) Respective CT images of overall

attenuation, showing from left to right, heterogeneous, mixed, and homogeneous and hypoattenuating. (b) Respective CT images of tumor-liver interface, showing from left to right, ill-defined, variable, and sharp. (c) Respective CT images of peripheral rim enhancement, showing from left to right, present; if initially present, partially resolved; and, if initially present, completely resolved.

Fig. 2. Representative histological findings of colorectal liver metastases after preoperative chemotherapy demonstrating (a) usual necrosis, (b) infarct-like necrosis, (c) dangerous halo, (d) three zonal change, and (e) mucous lake. Hematoxylin & eosin-stained section (a, b, x200; c, 20x; d, 100x; e, 40x).

Fig. 3. Representative shape of infarct-like necrosis of colorectal liver metastases after preoperative chemotherapy. Microscopic images showing (a) central infarct-like necrosis and (b) speckled infarct-like necrosis. Hematoxylin & eosin-stained section (a, b, loupe).

Fig. 4. Summary of the correlation between morphologic appearance on CT and histologic findings of colorectal liver metastasis after preoperative chemotherapy.

Parameter	Preoperative chemotherapy, N = 47		
	5-FU	FOLFOX[†] or FOLFIRI[†]	FOLFOX or FOLFIRI with BV[†]
Number of cases	12	9	26
Median age (range), years	70 (48-82)	61 (58-78)	64.5 (41-79)
Male:Female ratio	4:8	8:1	19:7
Synchronous:Metachronous metastases	0:12	0:9	9:17
Median number of metastases (range)	1 (1-2)	2 (1-5)	3 (1-11)
Median diameter of largest metastasis (range), mm	24 (20-65)	23 (9-67)	23 (7-155)

Table 1 Clinicopathologic characteristics of patients treated with preoperative chemotherapy for colorectal liver metastases.

[†]Footnote: 5-FU with leucovorin and oxaliplatin, FOLFOX; 5-FU with leucovorin and irinotecan, FOLFIRI; Bevacizumab, BV.

	Overall attenuation on CE-CT†			
Histologic finding	Heterogeneous, N = 16	Mixed, N = 13	Homogenous, N = 18	*P* value
Usual necrosis†	16 (100%)	10 (76.9%)	13 (72.2%)	*P* = 0.078
Infarct-like necrosis†	6 (37.5%)	8 (61.5%)	12 (66.7%)	*P* > 0.1
Three zonal change	7 (43.8%)	5 (38.5%)	12 (66.7%)	*P* > 0.1
Dangerous halo	9 (56.3%)	8 (61.5%)	9 (50.0%)	*P* > 0.1
Mucous lake	0 (0%)	5 (38.5%)	5 (27.8%)	*P* = 0.029*
Shape of infarct-like necrosis				
Central infarct-like necrosis	1 (6.3%)	6 (46.2%)	7 (38.9%)	*P* > 0.1
Speckled infarct-like necrosis	4 (25.0%)	2 (15.4%)	5 (27.8%)	
Others	1 (6.3%)	0 (0%)	0 (0%)	
None of infarct-like necrosis	10 (62.5%)	5 (38.5%)	6 (33.3%)	
Dominant type of necrosis				
Usual necrosis	12 (75.0%)	5 (38.5%)	4 (22.2%)	*P* = 0.011*
Infarct-like necrosis	4 (25.0%)	8 (61.5%)	11 (61.1%)	
None of necrosis	0 (0%)	0 (0%)	3 (16.7%)	
Presence of viable tumor cells				
0-10%	0 (0%)	1 (7.7%)	4 (22.2%)	*P* = 0.064
11-50%	3 (18.8%)	6 (46.2%)	7 (38.9%)	
51-100%	13 (81.3%)	6 (46.2%)	7 (38.9%)	

Table 2 Correlation between CT overall attenuation and histologic findings.

†Footnote: contrast-enhanced computed tomography, CE-CT.

*Significantly different between the three radiological findings of overall attenuation ($P < 0.05$).

	Tumor-liver interface on CE-CT†			
Histologic finding	Ill-defined, N = 17	Variable, N = 18	Sharp, N = 12	*P* value
Usual necrosis	17 (100%)	13 (72.2%)	9 (75.0%)	*P* = 0.064
Infarct-like necrosis	6 (35.3%)	10 (55.6%)	10 (83.3%)	*P* = 0.038*
Three zonal change	8 (47.1%)	8 (44.4%)	8 (66.7%)	*P* > 0.1
Dangerous halo	11 (64.7%)	11 (61.1%)	4 (33.3%)	*P* > 0.1
Mucous lake	2 (11.8%)	7 (38.9%)	1 (8.3%)	*P* = 0.066
Shape of infarct-like necrosis				
Central infarct-like necrosis	2 (11.8%)	7 (38.9%)	5 (41.7%)	*P* > 0.1
Speckled infarct-like necrosis	4 (23.5%)	3 (16.7%)	4 (33.3%)	
Others	0 (0%)	0 (0%)	1 (8.3%)	
None of infarct-like necrosis	11 (64.7%)	8 (44.4%)	2 (16.7%)	
Dominant type of necrosis				
Usual necrosis	11 (64.7%)	7 (38.9%)	3 (25.0%)	*P* > 0.1
Infarct-like necrosis	6 (35.3%)	9 (50.0%)	8 (66.7%)	
None of necrosis	0 (0%)	2 (11.1%)	1 (8.3%)	
Presence of viable tumor cells				
0-10%	0 (0%)	0 (0%)	5 (41.7%)	*P* = 0.0003*
11-50%	4 (23.5%)	10 (55.6%)	2 (16.7%)	
51-100%	13 (76.5%)	8 (44.4%)	5 (41.7%)	

Table 3 Correlation between CT tumor-liver interface and histologic findings.

†Footnote: contrast-enhanced computed tomography, CE-CT.

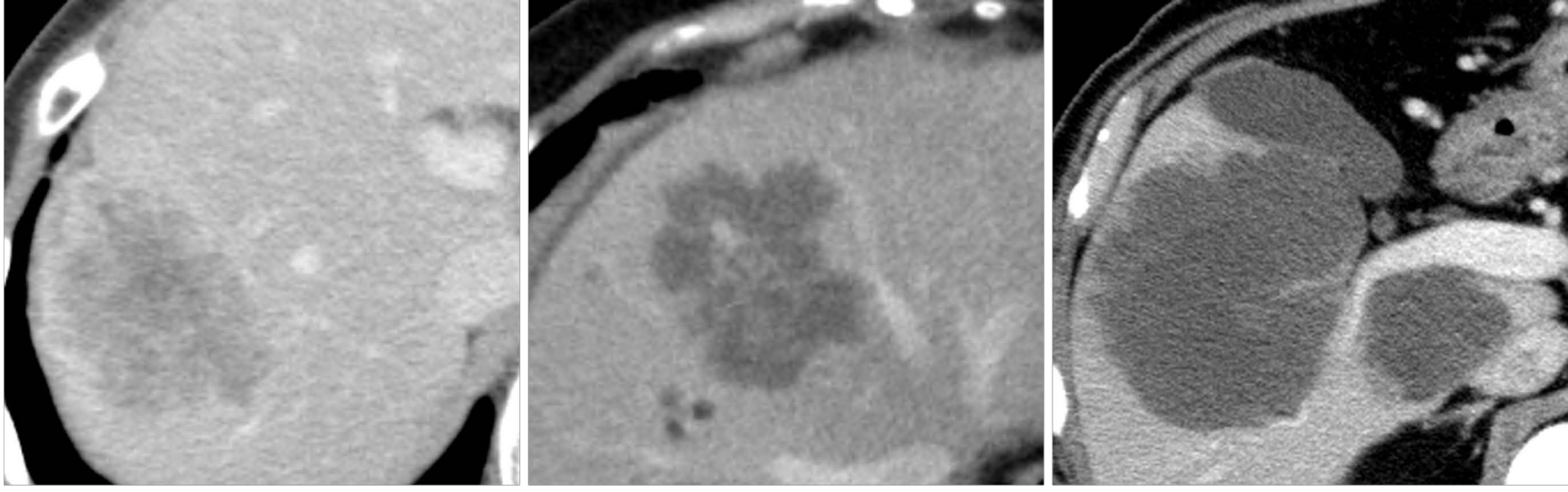
*Significantly different between the three radiological findings of overall attenuation ($P < 0.05$).

	Peripheral rim enhancement on CE-CT[†]			
Histologic finding	Present, N = 16	Partially resolved, N = 18	Completely resolved, N = 13	*P* value
Usual necrosis	16 (100%)	15 (83.3%)	8 (61.5%)	$P = 0.023^{*}$
Infarct-like necrosis	8 (50.0%)	9 (50.0%)	9 (69.2%)	$P > 0.1$
Three zonal change	8 (50.0%)	8 (44.4%)	8 (61.5%)	$P > 0.1$
Dangerous halo	8 (50.0%)	13 (72.2%)	5 (38.5%)	$P > 0.1$
Mucous lake	2 (12.5%)	5 (27.8%)	3 (23.1%)	$P > 0.1$
Shape of infarct-like necrosis				
Central infarct-like necrosis	3 (18.8%)	6 (33.3%)	5 (38.5%)	$P > 0.1$
Speckled infarct-like necrosis	5 (31.3%)	2 (11.1%)	4 (30.8%)	
Others	0 (0%)	1 (5.6%)	0 (0%)	
None of infarct-like necrosis	8 (50.0%)	9 (50.0%)	4 (30.8%)	
Dominant type of necrosis				
Usual necrosis	8 (50.0%)	10 (55.6%)	3 (23.1%)	$P > 0.1$
Infarct-like necrosis	8 (50.0%)	7 (38.9%)	8 (61.5%)	
None of necrosis	0 (0%)	1 (5.6%)	2 (15.4%)	
Presence of viable tumor cells				
0-10%	0 (0%)	0 (0%)	5 (38.5%)	$P = 0.004^{*}$
11-50%	6 (37.5%)	6 (33.3%)	4 (30.8%)	
51-100%	10 (62.5%)	12 (66.7%)	4 (30.8%)	

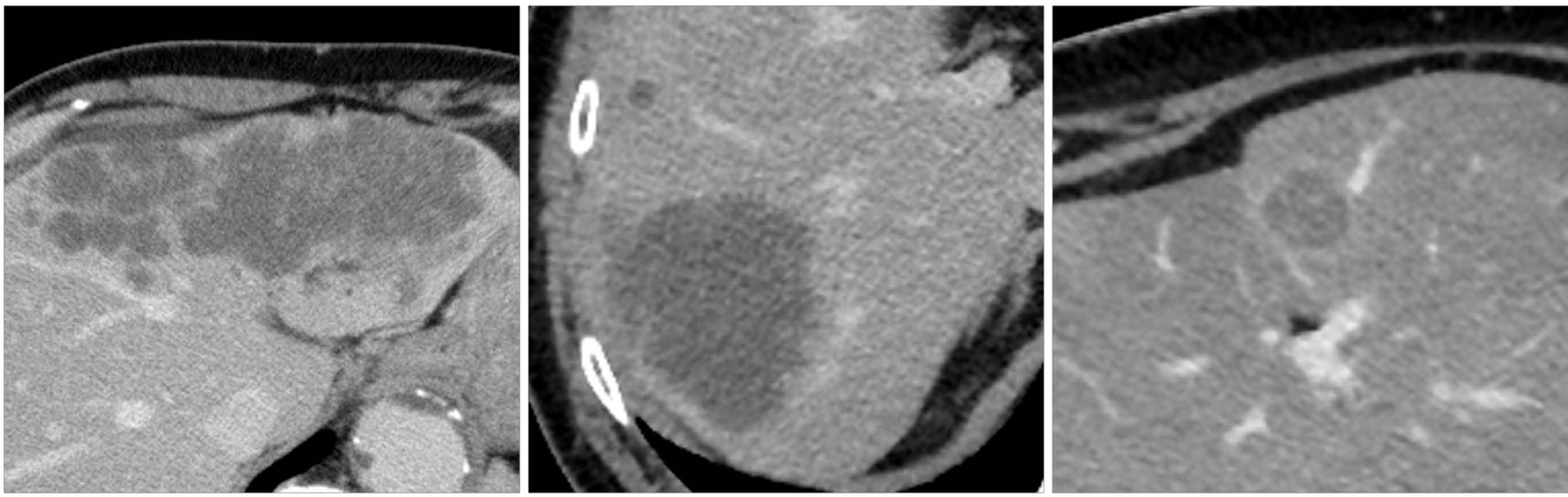
Table 4 Correlation between CT peripheral rim enhancement and histologic findings.

[†]Footnote: contrast-enhanced computed tomography, CE-CT.

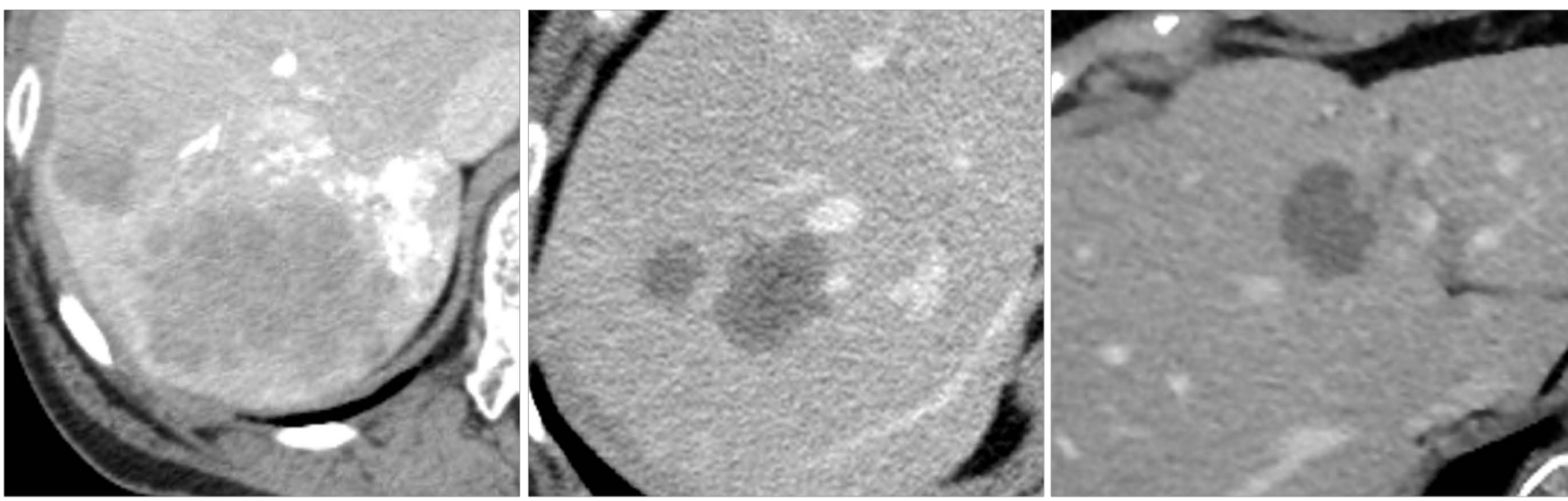
*Significantly different between the three radiological findings of overall attenuation ($P < 0.05$).



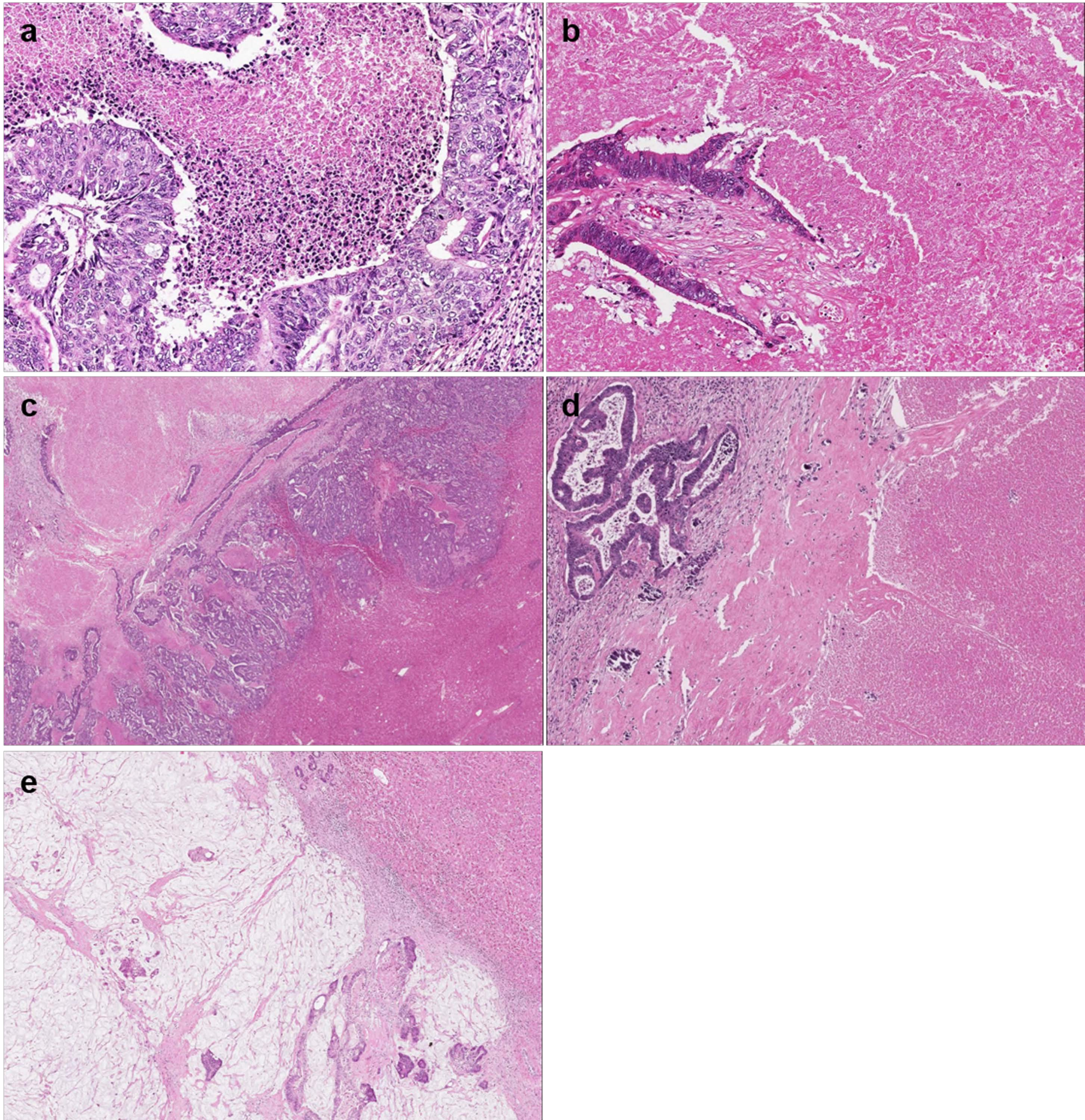
a.

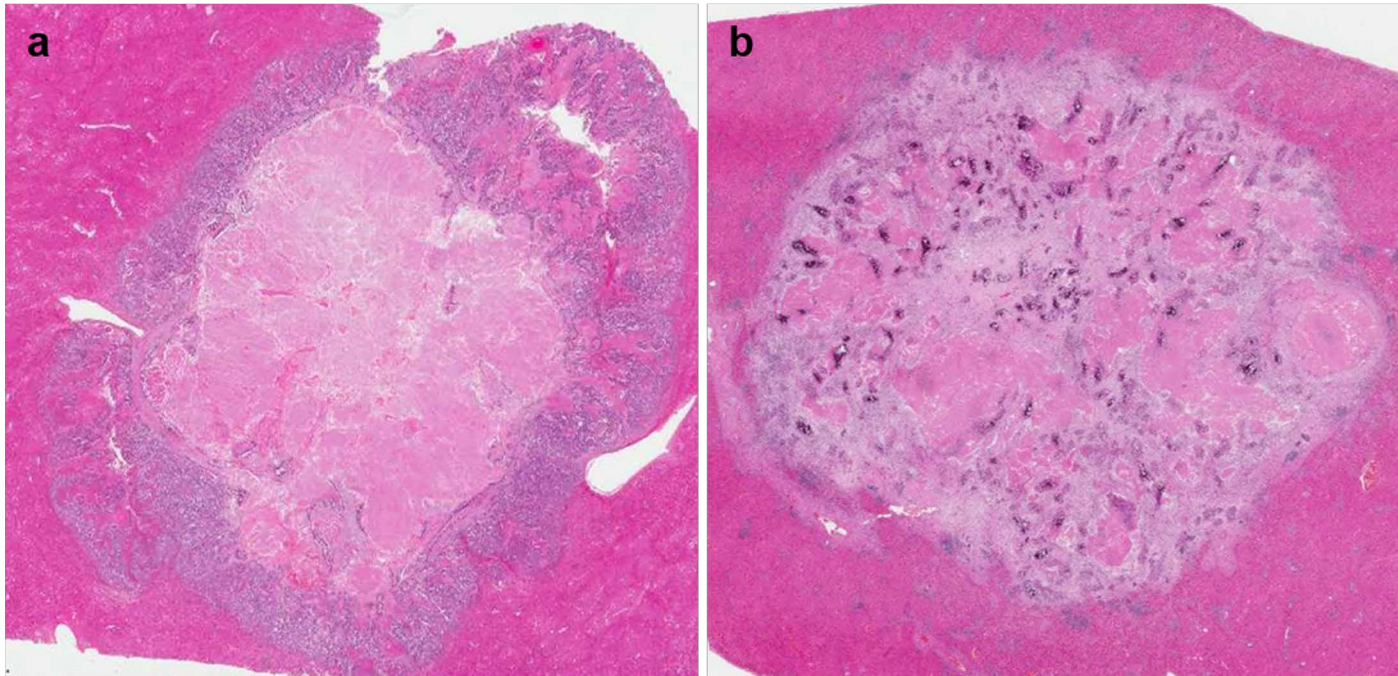


b.



c.


a
b
c
d
e


a
b

Morphologic criterion on CT	⟺	Histological findings
✓ Overall attenuation		Dominant type of necrosis (Heterogenous → Mixed) Mucous lake
✓ Tumor–liver interface		Infarct-like necrosis Viable tumor cells
✓ Peripheral rim of enhancement		Usual necrosis Viable tumor cells (Partially resolved → Completely resolved)