

# Incidence and computed tomography findings of lenvatinib-induced pancreatobiliary inflammation

## A single-center, retrospective study

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### Abstract

In this single-center retrospective study, we intended to evaluate the frequencies and characteristics of computed tomography findings of pancreatobiliary inflammation (PBI) in patients treated with lenvatinib and the relationship of these findings with treatment-planning changes.

We included 78 patients (mean  $\pm$  standard deviation, 69.8  $\pm$  9.4 years, range: 39–84 years, 62 men) with hepatocellular carcinoma (n=62) or thyroid carcinoma (n=16) who received lenvatinib (June 2016–September 2020). Two radiologists interpreted the posttreatment computed tomography images and assessed the radiological findings of PBI (symptomatic pancreatitis, cholecystitis, or cholangitis). The PBI effect on treatment was statistically evaluated.

PBI (pancreatitis, n=1; cholecystitis, n=7; and cholangitis, n=2) was diagnosed in 11.5% (9/78) of the patients at a median of 35 days after treatment initiation; 6 of 9 patients discontinued treatment because of PBI. Three cases of cholecystitis and 1 of cholangitis were accompanied by gallstones, while the other 5 were acalculous. The treatment duration was significantly shorter in patients with PBI than in those without (median: 44 days vs. 201 days,  $P=.02$ ). Overall, 9 of 69 patients without PBI showed asymptomatic gallbladder subserosal edema.

Lenvatinib-induced PBI developed in 11.5% of patients, leading to a significantly shorter treatment duration. Approximately 55.6% of the PBI cases were acalculous. The recognition of this phenomenon would aid physicians during treatment planning in the future.

**Abbreviations:** AGSE = asymptomatic gallbladder subserosal edema, CT = computed tomography, PBI = pancreatobiliary inflammation, uHCC = unresectable hepatocellular carcinoma, uTC = unresectable thyroid carcinoma.

**Keywords:** computed tomography, hepatocellular carcinoma, lenvatinib, pancreatobiliary inflammation, thyroid carcinoma

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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## 1. Introduction

Multikinase inhibitors are cancer treatment drugs that inhibit angiogenesis and other pathways related to cancer progression and metastasis.<sup>[1]</sup> Lenvatinib (Lenvima; Eisai Co, Tokyo, Japan) is a novel anti-angiogenic multikinase inhibitor indicated for unresectable hepatocellular carcinoma (uHCC) and unresectable thyroid cancer (uTC).<sup>[2,3]</sup> Compared with its prior-generation drug, sorafenib, lenvatinib showed a higher objective response, reflecting its higher antiangiogenic activity, in a phase-3 randomized controlled trial for uHCC.<sup>[4]</sup> Significantly longer progression-free survival has been reported in patients with uTC.<sup>[5]</sup> One important issue with multikinase inhibitors is the high incidence of adverse effects, frequently resulting in treatment discontinuation or drug alteration. Several studies have reported that approximately 20% of the patients receiving lenvatinib have to discontinue the drug because of adverse events.<sup>[2,6,7]</sup>

Some authors have reported cases of pancreatobiliary inflammation (PBI), namely pancreatitis<sup>[4,8]</sup> and cholecystitis,<sup>[9]</sup> observed in patients receiving lenvatinib treatment. These complications may preclude the continuation of lenvatinib treatment, potentially leading to poor patient prognosis. However, their frequencies, radiological characteristics, and treatment effects have not been established. To fill this knowledge gap, we aimed to evaluate the frequencies and characteristics of the computed tomography (CT)

findings of PBI due to lenvatinib treatment and their relationship with treatment-planning changes.

## 2. Materials and methods

This single-center retrospective study was approved by the local ethics committee (blinded for review) of our hospital and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived owing to the retrospective design of the study. The privacy of all patients was fully protected.

### 2.1. Patients

We searched for data of patients who had received lenvatinib and underwent abdominal CT between June 2016 and September 2020 using the hospital's search system and identified 97 consecutive patients. Of these, 77 patients received lenvatinib for uHCC and 21 received lenvatinib for uTC. Patients without pre- or post-treatment CT data were excluded ( $n=19$ ). Finally, 78 patients (uHCC,  $n=62$ ; uTC,  $n=16$ ) were included, and their data were further evaluated. PBI was diagnosed when symptoms were accompanied by CT findings of pancreatitis, cholecystitis, or cholangitis. The symptoms and CT findings required to diagnose PBI are described in the **Radiological Assessment** section.

### 2.2. CT acquisition

Abdominal CT was performed using a 16 to 320-row multi-detector CT unit (Aquilion LB, Aquilion PRIME, Aquilion ONE, Aquilion Precision; Canon, Tochigi, Japan; Revolution CT,

Discovery CT750 HD; GE, Tokyo, Japan) with the following parameters: tube voltage, 120 to 140 kVp; effective current, 95 to 667 mA; spiral pitch factor, 0.813 to 1.375; helical pitch, 63 to 127; field of view, 35 to 45 cm; matrix size,  $512 \times 512$ . Acquisition parameters were modified to minimize patient radiation exposure while maintaining sufficient resolution for abdominal CT evaluation. A 1.05.0-mm gapless section was reconstructed before being reviewed on the picture archiving and communication system monitor. A total of 78 and 243 pre- and posttreatment CT examinations were respectively performed. Posttreatment contrast-enhanced CT was performed 159 times in 61 patients, while the other 17 patients only underwent unenhanced CT in all examinations. The indications for the CT examinations are summarized in Table 1.

### 2.3. Clinical data

The following data were collected from the medical records: patient demographics, presence or absence of fever or abdominal symptoms indicating PBI, and laboratory data for routine evaluation during lenvatinib treatment including white blood cell count, serum C-reactive protein, gamma glutamyl transpeptidase, alkaline phosphatase, aspartate transaminase, alanine transaminase, total bilirubin, amylase, and lipase levels. Each laboratory value was considered to be elevated when the following criteria were met<sup>[10]</sup>: white blood cell count (reference range, 3300–8600/ $\mu\text{L}$ ),  $> 10,000/\mu\text{L}$ ; eosinophil count (reference range,  $< 8.5\%$  of white blood cell),  $> 500/\mu\text{L}$ ; C-reactive protein ( $< 0.3 \text{ mg/dL}$ ),  $\geq 1 \text{ mg/dL}$ ; gamma glutamyl transpeptidase (male: 13–64 U/L; female: 9–32 U/L),  $> 96 \text{ U/L}$  (male), and  $> 48 \text{ U/L}$  (female); alkaline phosphatase (The International

**Table 1**  
Demographics and clinical characteristics of the study population.

Parameter	Total (n=78)	With PBI (n=9)	Without PBI (n=69)	P value
Age (yr, mean $\pm$ standard deviation [range])	69.8 $\pm$ 9.4 (39–84)	68.7 $\pm$ 10.5 (50–80)	69.9 $\pm$ 9.4 (39–61)	.86
Sex, n (%)				.68
Male	62 (79.5%)	8 (88.9%)	54 (78.3%)	
Female	16 (20.5%)	1 (11.1%)	15 (21.7%)	
Malignancy, n (%)				$> .99$
uHCC	62 (79.5%)	7 (77.8%)	55 (79.7%)	
uTC	16 (20.5%)	2 (22.2%)	14 (20.3%)	
Lenvatinib: initiation dose (mg/dL, median [range])				.27
uHCC	12 (4–12)	8 (4–12)	12 (4–12)	
uTC	24 (8–24)	15 (10–20)	24 (8–24)	
Lenvatinib: treatment duration, (d, median [range])	183.5 (2–1629)	44 (23–374)	201 (2–1629)	.02*
PB complications observed on CT during lenvatinib treatment, n (patients, %)				
Pancreatitis	1 (1.3%) <sup>†</sup>			
Cholecystitis	7 (9.0%) <sup>†</sup>			
Cholangitis	2 (2.6%)			
Asymptomatic subserosal gallbladder edema	9 (11.5%)			
Period from lenvatinib initiation to appearance of on CT (d, median [range])	35 (7–355)			
Indications for CT performed during lenvatinib treatment (n=243, patient, %)				
Follow-up	208 (85.6%)			
Abdominal pain	13 (5.3%)			
Fever	11 (4.5%)			
Respiratory distress	2 (0.8%)			
Decreased appetite	1 (0.4%)			
Back pain	1 (0.4%)			
Others	7 (2.9%)			

CT=computed tomography, PBI=pancreatobiliary inflammation, uHCC=unresectable hepatocellular carcinoma, uTC=unresectable thyroid carcinoma.

\*Statistically significant.

<sup>†</sup>One patient had both pancreatitis and cholecystitis.

Federation of Clinical Chemistry and Laboratory Medicine: 38–113 U/L; Japan Society of Clinical Chemistry: 106–322 U/L), > 226 U/L (The International Federation of Clinical Chemistry and Laboratory Medicine) or > 433 U/L (Japan Society of Clinical Chemistry); aspartate transaminase (13–30 U/L), > 45 U/L; alanine transaminase (male: 10–42 U/L; female: 7–23 U/L), > 63 U/L (male) and > 34.5 U/L (female); total bilirubin (0.4–1.5 mg/dL),  $\geq$  2 mg/dL; amylase (44–132 U/L), > 132 U/L; and lipase (16–49 U/L), > 49 U/L. The white blood cell count, eosinophil count, and C-reactive protein level were collected in cases where the CT findings suggested PBI.

#### 2.4. Radiological assessment

All CT scans were analyzed by 2 diagnostic radiologists with 7 and 5 years of experience in abdominal radiology, respectively (the first being a board-certified diagnostic radiologist and the second a board-certified radiologist), who were blinded to patient information, including whether the patients had symptoms or not. CT findings suggestive of pancreatitis included focal or diffuse parenchymal enlargement, changes in the density of parenchyma due to edema, indistinct pancreatic margins due to inflammation, surrounding retroperitoneal fat stranding, and/or lack of parenchymal enhancement.<sup>[11]</sup> Pancreatitis was diagnosed based on the presence of these CT findings as well as at least one of the following symptoms: abdominal pain consistent with the disease and/or biochemical evidence of pancreatitis (serum amylase and/or lipase greater than three times the upper limit of normal).<sup>[12,13]</sup> CT findings suggestive of cholecystitis included gallbladder distention, gallbladder wall thickening, thickening of the gallbladder mucosa, increased enhancement of the liver parenchyma adjacent to the gallbladder in the post-contrast arterial phase, pericholecystic fluid, and/or a linear hyperdense area in the pericholecystic fat tissue.<sup>[14]</sup> Cholecystitis was diagnosed based on the presence of these CT findings as well as on at least one of the following symptoms: local signs of inflammation (Murphy sign and/or right upper quadrant mass/pain/tenderness) or systemic signs of inflammation (fever, elevated C-reactive protein, and/or white blood cell count).<sup>[10]</sup> CT findings suggestive of cholangitis included transient hyperattenuation differences in the arterial phase, cholangiectasis, and/or increased enhancement and/or wall thickening of the bile duct.<sup>[10,15]</sup> Cholangitis was diagnosed based on the presence of these CT findings as well as on at least one of the following symptoms: systemic inflammation (fever, shaking chills, and/or inflammatory response on laboratory examination), jaundice, or abnormal liver function test results.<sup>[10]</sup> In addition to PBI, the presence or absence of gallbladder subserosal edema and of gallstones and whether the patients had undergone cholecystectomy were also investigated.

#### 2.5. Statistical analysis

Differences in the frequencies of treatment discontinuation and treatment duration of lenvatinib were compared between patients with and without PBI, as confirmed on CT, using the Mann–Whitney *U* test and Fisher exact test. Patient background variables were also compared between the 2 groups using the *t* test, Mann–Whitney *U* test, or Fisher exact test, as appropriate. Family-wise error correction for multiple comparisons was performed using the Bonferroni method. All *P* values corresponded to 2-sided tests, and the statistical significance level was

set at  $P < .05$ . Statistical analyses were performed using JMP Pro (version 15.0.0; SAS Institute, Cary, NC).

### 3. Results

The demographics and clinical characteristics of the study population are summarized in Table 1. The mean age of the patients was  $69.8 \pm 9.4$  (years, mean  $\pm$  standard deviation; range, 39–84 years); 62 (79.5%) patients were men, and 62 (79.5%) patients had uHCC. Lenvatinib treatment was initiated at a median dose of 12 mg/d for uHCC and 24 mg/d for uTC, depending on the patient's body weight. No patient showed findings of PBI on the pretreatment CT.

#### 3.1. Clinical findings

During the course of lenvatinib treatment, CT findings suggestive of PBI were seen in 9 of 78 patients (11.5%): pancreatitis,  $n = 1$  (1.3%; 1 patient also had cholecystitis); cholecystitis,  $n = 7$  (9.0%; 1 patient also had pancreatitis); and cholangitis,  $n = 2$  (2.6%). Two patients were diagnosed with cholecystitis based on the analysis of unenhanced CT findings. All these patients were symptomatic and then diagnosed with PBI. The median onset of PBI was 35 days (range, 7–355 days) after the initiation of lenvatinib treatment. At the time of PBI diagnosis, the elevation of serum ALT and total bilirubin levels was significantly greater in patients with PBI than in those without (ALT, 9/9 [100%] vs 20/67 [29.9%],  $P < .001$ ; total bilirubin, 8/9 [88.9%] vs 13/67 [19.4%],  $P < .001$ ). Eosinophilia was not observed in any patient with PBI. The frequency of treatment discontinuation tended to be higher in patients with PBI than in those without (8/9 [88.9%] vs 43/69 [62.3%],  $P = .15$ ). PBI was the direct cause of treatment discontinuation in 6 cases (55.6%). The duration of lenvatinib treatment was significantly shorter in patients with PBI than in those without (median duration of lenvatinib treatment: 44 days vs 201 days,  $P = .02$ ). The results are summarized in Table 2.

#### 3.2. Radiological findings

Gallstones were found in 21 of 78 patients (26.9%) on both pre- and posttreatment CT without increase or decrease in the number of gallstones. One patient with PBI and 25 patients without PBI underwent cholecystectomy before the pretreatment CT. Among the 9 patients with PBI, 3 cases of cholecystitis (33.3%; uHCC,  $n = 1$ ; uTC,  $n = 2$ ) and 1 case of cholangitis (with uHCC) were accompanied by gallstones, while the other 5 PBI cases (55.6%) were acalculous. The risk ratio of gallstones to PBI was 1.48. In the case of pancreatitis, the pancreas was diffusely enlarged, and surrounding retroperitoneal fat stranding was observed (Fig. 1A). In patients with acalculous cholecystitis, enlargement of the gallbladder and increased enhancement of the gallbladder wall were observed (Fig. 1B). In the cases of cholangitis, the bile ducts were enlarged, and the walls of the bile ducts were increasingly enhanced (Fig. 1C and D). These CT findings were also found in cholecystitis and cholangitis cases with gallstones. Perforation of the gallbladder wall was not observed in any patient. Among those who did not satisfy the diagnostic criteria for PBI, 9 of 69 patients (13.0%) showed asymptomatic gallbladder subserosal edema (AGSE, Fig. 2). Two patients were diagnosed with AGSE based on analysis of unenhanced CT findings. The average period from lenvatinib initiation to the detection of AGSE on CT was  $72.7 \pm 108.3$  days (range, 7–355 days).

**Table 2**  
**Clinical findings.**

		With PBI	Without PBI	P value (Fisher exact test)
Treatment discontinuation (n, %)		8/9 (88.9%)	43/68 (63.2%)	.15
Abnormal laboratory findings (n, %)	Criteria (serum)			
Gamma glutamyl transpeptidase	> 96 U/L	7/9 (77.8%)	28/67 (41.8%)	.072
Alkaline phosphatase	> 226 U/L (IFCC) > 433 U/L (JSCC)	6/9 (66.7%)	26/67 (38.8%)	.15
Aspartate transaminase	> 45 U/L	9/9 (100%)	37/67 (55.2%)	.0097
Alanine transaminase		9/9 (100%)	20/67 (29.9%)	< .0001*
Total bilirubin	≥ 2.0 mg/dL	8/9 (88.9%)	13/67 (19.4%)	< .0001*
Amylase	> 132 U/L	2/8 (25.0%)	4/58 (6.9%)	.15
Lipase	> 49 U/L	2/3 (66.7%)	n/a	

IFCC=The International Federation of Clinical Chemistry and Laboratory Medicine, JSCC=Japan Society of Clinical Chemistry, PBI=pancreatobiliary inflammation.

\*Statistically significant.

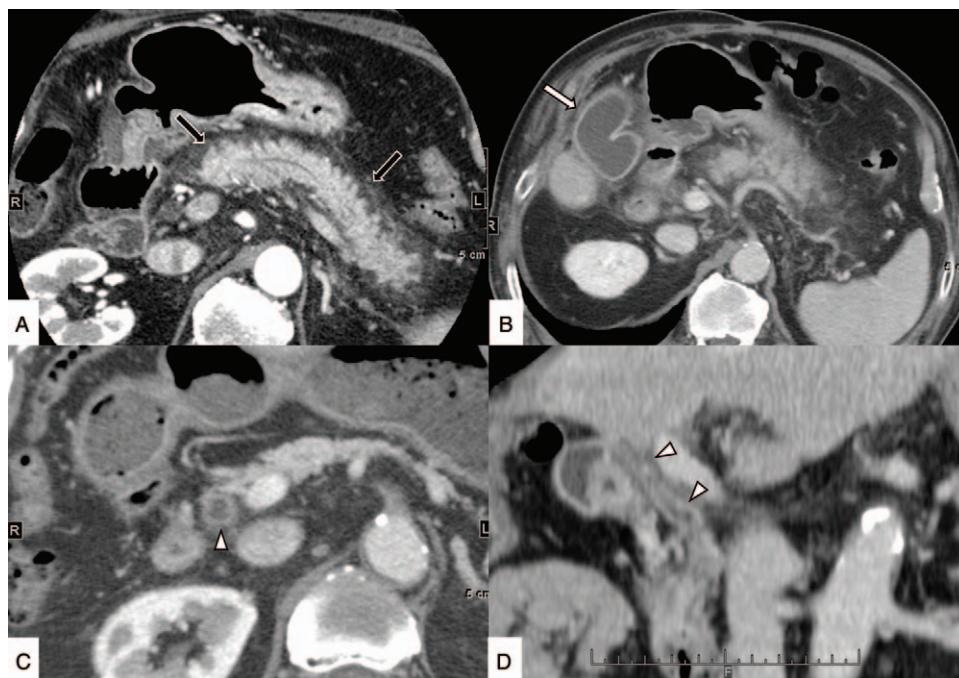
A total of 6/9 cases (66.7%) of AGSE were acalculous, and the CT findings improved in 7/9 patients (77.8%) after dose reduction of lenvatinib, while no follow-up CT was performed for the remaining 2 patients.

#### 4. Discussion

In this study, we evaluated the frequencies and characteristic CT findings of PBI and their association with treatment-planning changes. To the best of our knowledge, this was the first study to evaluate these factors and their effect on lenvatinib treatment. Particularly, we found that PBI was observed in 9 of 78 (11.5%) patients receiving lenvatinib at a median of 35 days after the

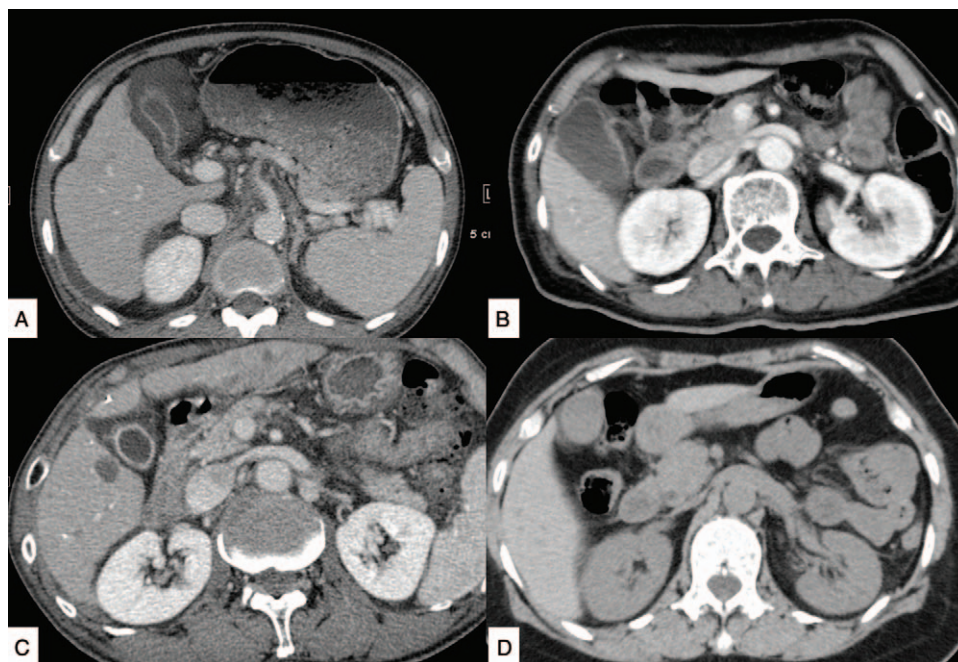
initiation of treatment. Treatment was discontinued in 8 of 9 (88.9%) patients, and the duration of lenvatinib treatment was significantly shorter in patients with PBI than in those without. Three cases of cholecystitis and 1 case of cholangitis were accompanied by gallstones, while the other 5 PBI cases were acalculous. AGSE was found in 9 of 69 (13.0%; uHCC, n=5; uTC, n=4) patients without PBI.

Kawakami et al<sup>[8]</sup> reported a case of lenvatinib-induced pancreatitis without gallbladder stones observed 19 months after the initiation of lenvatinib treatment in a patient with stage IV follicular thyroid carcinoma. Tyrosine kinase inhibitor-induced pancreatitis has also been reported, with a reported frequency of 0% to 4.3% in patients receiving these drugs.<sup>[16]</sup> The mechanisms



**Figure 1.** Representative cases of acalculous pancreatobiliary inflammation. A and B, Contrast-enhanced axial CT image of a 71-year-old man with abdominal pain. The patient had started lenvatinib treatment 11 weeks previously for uHCC. The CT image shows an enlarged pancreas with surrounding fat stranding (black arrows). The patient also had acalculous cholecystitis. The CT image shows an enlarged gallbladder with a thickened wall and surrounding fat stranding (white arrow). C and D, Contrast-enhanced axial and coronal images of an 80-year-old man with abdominal pain. The patient had started lenvatinib treatment 3 weeks prior for uHCC. The CT image shows a thickened bile duct with increased enhancement of the wall (arrowheads). CT=computed tomography, uHCC=unresectable hepatocellular carcinoma.





**Figure 2.** Representative cases of asymptomatic subserosal gallbladder edema. Contrast-enhanced axial CT images (A–C) and unenhanced axial CT image (D) show subserosal gallbladder edema. All these patients were asymptomatic, and therefore, did not meet the criteria for pancreatitis, cholecystitis, or cholangitis. CT = computed tomography.

of multikinase-inhibitor- and tyrosine kinase inhibitor-induced pancreatitis are unknown. One explanation is that microvascular ischemia induced by these inhibitors can lead to autolytic enzyme release.<sup>[8]</sup> In the present study, acalculous pancreatitis was found in 1 patient (1.3%) 85 days after the initiation of lenvatinib treatment; this incidence is comparable to that previously reported.<sup>[16]</sup>

Honda et al<sup>[9]</sup> reported a case of lenvatinib-induced acalculous cholecystitis, which repeatedly led to rupture of the gallbladder and resulted in discontinuation of lenvatinib treatment and subsequent patient death due to HCC progression. Ishigaki et al<sup>[17]</sup> also reported a case of repeated episodes of acute cholecystitis during lenvatinib treatment for refractory HCC. Drug-induced cholecystitis (with or without cholangitis) is reportedly associated with the multikinase inhibitors sunitinib<sup>[18–23]</sup> and sorafenib.<sup>[24]</sup> In a case reported by Aihara et al,<sup>[24]</sup> marked eosinophilia (white blood cell count: 10,500/ $\mu$ L; eosinophil level: 32.3%) was found, and the patient's symptoms drastically improved after 3 days of prednisolone treatment (500 mg/d). Their report concluded that sorafenib-induced cholecystitis could occur as an allergic reaction. In the present study, however, eosinophilia was not found in any patient with PBI; therefore, a nonallergic mechanism was suggested. One possible explanation could be disturbance of platelet–endothelial cell interactions due to vascular endothelial growth factor inhibition, which can disrupt normal endothelial cell homeostasis and lead to loss of vascular integrity and submucosal inflammation.<sup>[3,25]</sup>

All reported cases of PBI associated with lenvatinib and other multikinase inhibitors described above were acalculous. In the present study, 4/7 of cholecystitis and 1/2 of cholangitis cases were acalculous, while gallstones accompanied the other 3/7 cholecystitis and 1/2 cholangitis cases before the initiation of lenvatinib treatment. It is difficult to precisely differentiate whether the emergence of PBI during lenvatinib treatment in patients with gallstones was induced by lenvatinib or was a

coincidental complication. However, the possibility of coincidental complication is unlikely because of the much higher rate of PBI accompanied by gallstones in the present study. In patients with gallstones, the reported frequency of developing symptoms was 1% to 4% per year,<sup>[25,26]</sup> and acute cholecystitis and cholangitis accounted for 36% and 0.2%, respectively.<sup>[27]</sup> In the present study, considering that the number of patients with gallstones was 21 and the median duration of lenvatinib treatment was approximately half a year (183.5 days), the theoretical numbers of patients developing acute cholecystitis and cholangitis were approximately 0.038 to 0.15 and 0.00021 to 0.00084, respectively. These numbers are much lower than the actual numbers of patients with cholecystitis and cholangitis included in our study, at 3 and 1, respectively.

One notable finding of the current study was that treatment was discontinued in 8 of 9 patients (88.9%) with PBI, and in 6 of them directly because of PBI. This may explain the significantly shorter duration of lenvatinib treatment in patients with PBI than in those without. Another notable finding was AGSE, which was found in 9 of 69 (13.0%) of patients without PBI. Considering the high rate of PBI in patients receiving lenvatinib treatment and that AGSE disappeared after lenvatinib dose reduction, we believe that AGSE was a change caused by the use of lenvatinib. Although the mechanism is unclear, it has been reported that most patients receiving sunitinib, which is also a multikinase inhibitor, develop bowel wall edema.<sup>[28]</sup> It is possible that the same mechanisms may be implicated in lenvatinib-caused gallbladder edema and sunitinib-induced bowel wall edema, such as tissue ischemia caused by vascular endothelial growth factor inhibition. Further studies, including histopathological investigations with more cases, may establish the mechanism of AGSE as well as its clinical importance.

This study has several limitations. First, it was a single-center retrospective investigation, and multiple CT scanners were used.

Second, the patients' backgrounds and the dose of lenvatinib were not unified because of the retrospective design. Third, because we only examined PBI with abnormal CT findings, the true incidence of PBI may have been underestimated. Finally, the histopathological characteristics of PBI and AGSE were not evaluated. Further histopathological investigations are warranted.

## 5. Conclusion

The incidence of lenvatinib-induced PBI was 11.5%. Treatment discontinuation was decided more frequently and the duration of lenvatinib treatment was significantly shorter in patients with PBI than in those without. Most PBI cases were acalculous. AGSE was found in 13.0% of the patients without PBI. Recognition of this phenomenon is important for diagnostic radiologists and attending physicians for treatment planning in the future.

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## References

- [1] Ramakrishnan V, Timm M, Haug JL, et al. Sorafenib, a multikinase inhibitor, is effective in vitro against non-Hodgkin lymphoma and synergizes with the mTOR inhibitor rapamycin. *Am J Hematol* 2012;87:277–83.
- [2] Fleeman N, Houten R, Chaplin M, et al. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. *BMC Cancer* 2019;19:1209.
- [3] Cabanillas ME, Takahashi S. Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. *Semin Oncol* 2019;46:57–64.
- [4] Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163–73.
- [5] Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:621–30.
- [6] Approved drugs - lenvatinib (Lenvima). Available at: <https://paperpile.com/app/p/296e062e-2fbc-07b0-9405-b4db8ae84b70> Accessed February 5, 2021.
- [7] Lenvima I. lenvatinib. Available at: <https://paperpile.com/app/p/dfd38c36-a9d4-02a1-8d86-531597ad35ea> Accessed February 5, 2021.
- [8] Kawakami H, Kubota Y, Ban T, Shibata N, Hosokawa A. Lenvatinib-induced acute pancreatitis associated with a pancreatic pseudocyst and splenic pseudoaneurysms. *Pancreas* 2018;47:e34–5.
- [9] Honda S, Saito Y, Sawada K, Hasebe T, Nakajima S, Okumura T. Repeated perforation of the gallbladder in a patient with hepatocellular carcinoma receiving lenvatinib. *Intern Med* 2020;59:657–62.
- [10] Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 2018;25:41–54.
- [11] O'Connor OJ, McWilliams S, Maher MM. Imaging of acute pancreatitis. *AJR Am J Roentgenol* 2011;197:W221–5.
- [12] Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
- [13] Leppäniemi A, Tolonen M, Tarasconi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg* 2019;14:27.
- [14] Fidler J, Paulson EK, Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. *AJR Am J Roentgenol* 1996;166:1085–8.
- [15] Arai K, Kawai K, Kohda W, Tatsu H, Matsui O, Nakahama T. Dynamic CT of acute cholangitis: early inhomogeneous enhancement of the liver. *AJR Am J Roentgenol* 2003;181:115–8.
- [16] Pezzilli R, Fabbri D, Imbrogno A, Corinaldesi R. Tyrosine kinase inhibitors, pancreatic hyperenzymemia and acute pancreatitis: a review. *Recent Pat Inflamm Allergy Drug Discov* 2011;5:165–8.
- [17] Ishigaki K, Hamada T, Nakai Y, et al. Lenvatinib-induced acute acalculous cholecystitis in a patient with hepatocellular carcinoma. *Clin J Gastroenterol* 2020;13:568–71.
- [18] Ito T, Tori M, Hashigaki S, et al. Efficacy and safety of sunitinib in Japanese patients with progressive, advanced/metastatic, well-differentiated, unresectable pancreatic neuroendocrine tumors: final analyses from a Phase II study. *Jpn J Clin Oncol* 2019;49:354–60.
- [19] Furubayashi N, Negishi T, Hirata Y, Taguchi K, Nakamura M. Acute acalculous cholecystitis in patients with clear cell renal cell carcinoma treated with sunitinib: report of two cases. *J Clin Med Res* 2014;6:302–4.
- [20] de Lima Lopes G, Rocha Lima CM. Emphysematous cholecystitis in a patient with gastrointestinal stromal tumor treated with sunitinib. *Pharmacotherapy* 2007;27:775–7.
- [21] Gomez-Abuin G, Karam AA, Mezzadri NA, Bas CA. Acalculous cholecystitis in a patient with metastatic renal cell carcinoma treated with sunitinib. *Clin Genitourin Cancer* 2009;7:62–3.
- [22] da Fonseca LG, Barroso-Sousa R, Sabbaga J, Hoff PM. Acute acalculous cholecystitis in a patient with metastatic renal cell carcinoma treated with sunitinib. *Clin Pract* 2014;4:635.
- [23] Nakano K, Suzuki K, Morita T. Life-threatening acute acalculous cholecystitis in a patient with renal cell carcinoma treated by sunitinib: a case report. *J Med Case Rep* 2012;6:69.
- [24] Aihara Y, Yoshiji H, Yamazaki M, et al. A case of severe acalculous cholecystitis associated with sorafenib treatment for advanced hepatocellular carcinoma. *World J Gastrointest Oncol* 2012;4:115–8.
- [25] Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. *Nat Rev Cancer* 2007;7:475–85.
- [26] Sanders G, Kingsnorth AN. Gallstones. *BMJ* 2007;335:295–9.
- [27] Glasgow RE, Cho M, Hutter MM, Mulvihill SJ. The spectrum and cost of complicated gallstone disease in California. *Arch Surg* 2000;135:1021–7.
- [28] Cornelissen L, Claus F, Wolter P, et al. Incidence of bowel wall oedema on computed tomography exams and association with diarrhoea in renal cell carcinoma patients treated with sunitinib. *Eur Radiol* 2015;25:375–9.