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Retrospective Study**Screening for hilar biliary invasion in ampullary cancer patients**

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Abstract**BACKGROUND**

The treatment for ampullary cancer is pancreatoduodenectomy or local ampullectomy. However, effective methods for the preoperative investigation of hilar biliary invasion in ampullary cancer patients have not yet been identified.

AIM

To determine the necessity of and an appropriate method for investigating hilar biliary invasion of ampullary cancer.

METHODS

Among 43 ampullary cancer patients, 34 underwent endoscopic treatment ($n = 9$) or surgery ($n = 25$). The use of imaging findings (thickening and enhancement of the bile duct wall on contrast-enhanced CT (CECT), irregularity on endoscopic retrograde cholangiography (ERC), thickening of the entire bile duct wall on intraductal ultrasonography (IDUS), and partial thickening of the bile duct wall on IDUS) and

biliary biopsy results for diagnosing hilar biliary invasion of ampullary cancer was compared.

RESULTS

Hilar invasion was not observed in every patient. Among the patients who did not undergo biliary stent insertion, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results showed the highest accuracy (100%) for diagnosing hilar biliary invasion. However, each imaging method and biliary biopsy yielded some false-positive results.

CONCLUSION

Although some false-positive results were obtained with each method, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. However, hilar invasion of ampullary cancer is rare; therefore, the investigation of hilar biliary invasion of ampullary cancer might be unnecessary.

INTRODUCTION

The standard treatment for ampullary cancer is pancreatoduodenectomy. In addition, local surgical resection of the ampulla or endoscopic ampullectomy has been recently performed for ampullary cancer that does not invade the sphincter of Oddi [1-6]. To perform these treatments, an accurate assessment of the extent of biliary invasion is important. Although ampullary lesions show ductal invasion [7-9], hilar biliary invasion by ampullary lesions has not been reported. When a tumor advances to the hilar biliary duct, the extent of resection is modified accordingly.

The efficacy of contrast-enhanced CT (CECT), endoscopic retrograde cholangiography (ERC), and intraductal ultrasonography (IDUS) for diagnosing the horizontal progression of bile duct cancer has been reported [10-15]. The diagnostic accuracy of CECT for lateral extension of hilar biliary cancer has been reported to be 71-96% [13,14,16-

²³]. In addition, ERC following IDUS has been reported to be useful for diagnosing lateral extension of biliary ductal cancer [24-27]. The diagnostic accuracy of mapping biopsy for lateral extension of biliary ductal cancer has been reported to be 73.0-89.0% [28-31]. However, whether these methods are effective for investigating hilar invasion in ampullary cancer patients is unknown. In this study, we aimed to reveal the best method for diagnosing hilar invasion in ampullary cancer patients.

MATERIALS AND METHODS

Study design and ethics

This retrospective study aimed to identify an appropriate screening method for hilar biliary invasion of ampullary cancer. This study was approved by the Institutional Review Board of Fukushima Medical University (approval number: 2453).

Patients

This study enrolled 43 ampullary cancer patients who were treated at Fukushima Medical University between September 2009 and December 2020. Among them, 34 patients underwent resection by endoscopic treatment ($n = 9$) or surgery ($n = 25$) (Table 1). Endoscopic ampullectomy was performed when invasion into the muscular layer or bile and pancreatic ducts was not observed by ERC or IDUS. It was not necessary to obtain informed consent from the patients because this study was retrospective in design and used previously anonymized clinical data. All the patients agreed to the clinical examination and treatment by providing written consent; in the case of participants under 18 years of age, consent was obtained from a parent and/or legal guardian. The details of the study can be found on the homepage of Fukushima Medical University. All methods were carried out in accordance with relevant guidelines and regulations.

Examination items

The final diagnosis of hilar biliary invasion was determined according to histological diagnosis and the nonexistence of local recurrence during follow-up for more than six months. When the horizontal margin of the resected specimen was negative, hilar invasion was considered negative.

Useful methods for diagnosing hilar invasion were investigated in 34 ampullary cancer patients who underwent endoscopic therapy or surgery. The assessed imaging findings of hilar biliary invasion were thickening and enhancement of the bile duct wall on CECT (Figure 1a), irregularity on ERC (Figure 1b), thickening of the entire bile duct wall on IDUS (Figure 1c), and partial thickening of the bile duct wall on IDUS (Figure 1d). The usefulness of hilar biliary biopsy was also considered. Thickening of the bile duct wall on IDUS was defined as a diameter of the bile duct wall greater than 2 mm.

All imaging findings were evaluated by more than two pancreaticobiliary disease specialists. Endoscopic retrograde cholangiopancreatography (ERCP) was performed as follows. With the patient in a prone position, a duodenoscope was inserted after sufficient sedation was achieved with midazolam. When the duodenoscope reached the Vater papilla, biliary cannulation was initiated. Tumor progression was evaluated by using ERC, IDUS, and hilar biliary biopsy. It is difficult to observe the whole circumference of the bile duct wall by EUS. Therefore, the evaluation of hilar invasion by EUS was not considered in this study.

JF260 V, JF240, and TJF240 duodenoscopes (Olympus, Tokyo, Japan) were used. An MTW ERCP tapered catheter (MTW Endoskopie, Wesel, Germany) and Tandem XL cannula (Boston Scientific Japan, Tokyo, Japan) were used as the ERC catheters. Endo Jaw FB231K (Olympus) or Radial Jaw™ 4 Biopsy Forceps (Boston Scientific Japan) were used for biliary biopsy.

Post-ERC pancreatitis (PEP) and adverse events were diagnosed according to Cotton's criteria [32]. PEP was defined as an elevated serum amylase level more than three times the normal upper limit with abdominal pain for more than 24 h after ERC. In addition, all PEP patients were confirmed to have peripancreatic inflammation by CECT. The severity of PEP was categorized as follows: mild: extended hospitalization for 2-3 days;

moderate: extended hospitalization for 4-10 days; and severe: extended hospitalization for more than 10 days, hemorrhagic pancreatitis, and pseudocysts that required intervention. The severity of bleeding was categorized as follows: mild: clinical evidence of bleeding, hemoglobin decrease < 3 g/dL, and no need for transfusion; moderate: transfusion (4 units or less) and no angiographic intervention or surgery; and severe: transfusion (5 units or more) or intervention (angiographic or surgical).

Statistical analyses

The imaging findings and biliary biopsy results were compared with respect to their ability to diagnose hilar invasion of ampullary cancer by Fisher's exact test. The Bonferroni method and Holm method were used to adjust for multiple comparisons. EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) was used for statistical analysis. A *P* value < 0.05 was considered indicative of a significant difference.

RESULTS

Patient characteristics and treatment

The patient characteristics and treatment results are shown in Table 1. The mean age of the patients was 68.0 ± 11.1 years. There were 20 male patients and 14 female patients. The numbers of the different lesion stages were as follows: I: 16; II: 8; and III: 10. Disease stage was classified according to the Union for International Cancer Control classification 8th edition [33]. Four patients had already undergone biliary stent insertion in other hospitals. No histological hilar biliary invasion or local recurrence was observed in any patient.

Imaging findings and biopsy results of all patients

Among the methods explored for diagnosing hilar biliary invasion of ampullary cancer, hilar biliary irregularity on ERC showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT: 53.1% (17/32); irregularity on ERC:

89.7% (26/29); thickening of the entire bile duct wall on IDUS: 87.5% (21/24); partial thickening of the bile duct wall on IDUS 87.5% (21/24), biliary biopsy results 72.7% (8/11), P value < 0.01) (Figure 2a). The diagnostic accuracy of irregularity on ERC for hilar invasion of ampullary cancer was significantly higher than that of thickening and enhancement of the bile duct wall on CECT (P value = 0.02).

Comparisons of the various combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion revealed that the diagnostic accuracies of irregularity on ERC + biliary biopsy results (96.7% (29/30)), thickening of the entire bile duct wall on IDUS + biliary biopsy results (95.8% (23/24)), and partial thickening of the bile duct wall on IDUS + biliary biopsy results (95.8% (23/24)) were significantly higher than that of thickening and enhancement of the bile duct wall on CECT + biliary biopsy results (62.5% (20/32), P value < 0.01 , = 0.02, and = 0.02, respectively) (Figure 2b).

Imaging findings and biopsy of patients who had not received biliary duct stents

Partial thickening of the bile duct wall on IDUS showed the highest diagnostic accuracy among the explored methods (thickening and enhancement of the bile duct wall on CECT: 57.1% (16/28); irregularity on ERC: 88.0% (22/25); thickening of the entire bile duct wall on IDUS: 84.2% (16/19); partial thickening of the bile duct wall on IDUS 89.5% (17/19); biliary biopsy: 66.7% (6/9); P value < 0.035 but no significant differences in pairwise comparisons) (Figure 3a).

Among the investigated combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion of ampullary cancer, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT + hilar biliary biopsy results: 64.3% (18/28); irregularity on ERC + biliary biopsy results: 96.2% (25/26); thickening of the entire bile duct wall on IDUS + biliary biopsy results: 95.0% (19/20); partial thickening of the bile duct wall on IDUS + biliary biopsy results: 100% (20/20); P value < 0.01) (Figure 3b). The combination of irregularity on ERC and biliary biopsy results and the combination of partial thickening of the bile duct wall on IDUS

and biliary biopsy results each had a significantly higher diagnostic accuracy for hilar biliary invasion of ampullary cancer than the combination of thickening and enhancement of the bile duct wall on CECT and biliary biopsy results (P value = 0.027, 0.017).

Adverse events

The adverse events are listed in Table 2. Postendoscopic ampullectomy bleeding occurred in two patients. Both patients improved with endoscopic hemostasis and transfusion. PEP occurred in three patients, all of whom improved with conservative treatment.

DISCUSSION

In this study, we investigated appropriate methods for diagnosing hilar biliary invasion of ampullary cancer. Hilar biliary invasion was not observed in all ampullary cancer patients. Although some false-positive results were obtained with each method, the diagnostic accuracy of the combination of partial thickening of the bile duct wall on IDUS and hilar biliary biopsy results for hilar biliary invasion was 100% for patients without biliary stents. On the other hand, thickening and enhancement of the hilar bile duct wall on CECT was not effective for diagnosing this condition.

Ampullary cancer occasionally develops concurrently with upstream biliary ductal cancer [34,35]. However, as described in the introduction, hilar biliary invasion of resectable ampullary cancer has rarely been reported. In fact, hilar invasion of ampullary cancer was not observed in this study. In past reports that have described the results of treatment or surgery for ampullary cancer, pancreaticobiliary type, lymph node metastasis, advanced T stage, and large tumors were identified as risk factors for poor prognosis [36-41]. Hilar biliary invasion was not listed as a risk factor in these reports. Taking the risk of PEP into consideration, it is possible that investigation of hilar biliary invasion in ampullary cancer is not necessary.

Thickening of the bile duct wall on CECT has been reported in cholestasis caused by several diseases (for example, cholangitis, common bile duct stones, pancreatitis and malignant biliary stricture) [42]. In a past systematic review and meta-analysis, the diagnostic accuracy of CT for assessing the extent of bile duct invasion was 64-96% [13]. In this study, the diagnostic accuracy of CECT for assessing hilar biliary invasion of ampullary cancer was lower than that reported in a previous meta-analysis. Regarding the CECT findings of ampullary cancer, papillary bulging and organ invasion have been identified as predictive factors of tumor recurrence or poor survival [43]. However, hilar bile duct wall thickness was not mentioned in the associated study. Thickening and enhancement of the hilar bile duct wall on CECT was not useful. It is thought that ampullary cancer exists at the exit of the bile duct and that the tumors more often close the biliary duct than other biliary diseases. This closure leads to thickening of the hilar bile duct wall; however, in this study, ampullary cancer did not invade the hilar bile duct.

The diagnostic accuracy of IDUS was higher among those patients without biliary stents. Biliary drainage can cause thickening of the bile duct wall, and IDUS should be performed before biliary drainage. Thickening on the cancerous portion of the bile duct wall has been reported to be heterogeneous and partially protruded [24-27,44]. In this study, partial thickening of the bile duct wall on IDUS showed the best accuracy among the investigated methods for diagnosing hilar invasion of ampullary cancer in patients without a biliary stent. Naitoh *et al* [45] reported that bile duct wall thickening in the nonstricture region was unremarkable in bile duct cancer patients. However, false-positive cases (diameter of the hilar bile duct wall from 2-3.3 mm) were observed in this study. Therefore, the evaluation of the nonstricture portion on IDUS in patients with ampullary cancer is not believed to be equivalent to that in patients with common bile duct cancer. Therefore, the detection of partial thickening of the bile duct wall should be combined with other methods.

False-positive hilar biliary biopsy results were found in three cases. Although this number is low, such results might influence the operative method. Therefore, false

positives in hilar biliary biopsy should be avoided. Regarding the reason for these false positives, it is highly likely that biopsy forceps contact the ampullary cancer. The efficacy of cholangioscopy in diagnosing biliary lesions has been reported [46-56]. However, passing the ampullary cancer is difficult with cholangioscopy. To avoid contact of the biopsy forceps with the tumor and to improve the diagnostic accuracy of hilar biliary biopsy for ampullary cancer patients, biliary biopsy with a catheter that introduces biopsy forceps could be useful [30,31]. When biliary biopsy with a catheter is unavailable, the combination of biliary biopsy and IDUS should be considered.

² This study has some limitations. First, this was a retrospective study performed at a single institution. A multicenter prospective study is needed to verify the results of this study. Second, a few patients underwent all examinations (CECT, ERC, IDUS, and biliary biopsy). In future studies, a higher number of cases would be desirable. Third, as described above, ampullary cancer patients with hilar biliary invasion were not included in this study. To improve the false-negative rate, a study involving cases of hilar biliary invasion is needed.

CONCLUSION

Although false-positive results were obtained with each method, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. In addition, it is recommended that hilar biliary biopsy be performed through a catheter to avoid contamination from the cancer. However, hilar invasion of ampullary cancer is rare, and the risk of PEP from hilar investigation exists. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

ARTICLE HIGHLIGHTS

Research background

The standard treatment for ampullary cancer is pancreaticoduodenectomy or focal ampullectomy. Before resection, it is important to accurately diagnose the biliary

invasion of ampullary cancer. However, the method that accurately evaluates hilar invasion of ampullary cancer is unknown.

Research motivation

Several methods (CECT, ERC, IDUS, biliary biopsy) can be used to diagnose the range of ampullary cancer invasion. However, detailed data of these methods for diagnosing the biliary invasion range of ampullary cancer have not been previously reported. Therefore, presurgical examination is not established in ampullary cancer patients.

Research objectives

To reveal the necessity of hilar investigation in ampullary cancer and a useful method for diagnosing whether ampullary cancer invades the hilar biliary duct.

Research methods

Diagnosability was compared between CECT, ERC, IDUS, and biliary biopsy in ampullary cancer patients who underwent pancreaticoduodenectomy or focal ampullectomy.

Research results

The combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS was efficient for diagnosing hilar invasion of ampullary cancer.

Research conclusions

Although false positives were observed for each method, hilar invasion was appropriately diagnosed based on the combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS. However, hilar biliary invasion is rare in ampullary cancer. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

Research perspectives

The results of this study contribute to the establishment of a systematic method for diagnosing hilar invasion and selecting treatments for ampullary cancer patients.

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