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# Very early recurrence following pancreaticoduodenectomy in patients with ampullary cancer

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**Abstract**

We aimed to identify the factors for very early recurrence (within 6 months) of ampullary cancer following curative resection and to compare the immunohistochemical expression rate of various antibodies between the 2 main histologic subtypes of ampullary adenocarcinoma.

In this retrospective study, the postoperative outcomes and clinicopathologic factors for very early recurrence that occurred in 14 of 93 patients who underwent pancreaticoduodenectomy (PD) for ampullary adenocarcinoma between January 2002 and August 2014 were analyzed. Thereafter, we identified the factors associated with very early recurrence following surgery. Additionally, we compared the expression rates of CK7, CK20, MUC1, MUC2, MUC5AC, MUC6, S100P, and CDX2 between the 2 main histologic subtypes of ampullary adenocarcinoma (NCC2019-0138).

The patients who underwent PD for ampullary cancer were divided into 2 groups: very early recurrence and others. Compared with the other patients, the 14 patients (32.6%) who developed very early recurrence had shorter median disease-free survival (4.2 vs 49.7 months, $P = .001$) and overall survival (18.2 vs 113.7 months, $P < .001$). Large tumor, lymph node metastasis, and pancreatobiliary type were independently associated with very early recurrence of ampullary cancer following PD.

Large tumor, lymph node metastasis, and pancreatobiliary type were the independent risk factors for very early recurrence of ampullary cancer following curative resection. Therefore, ampullary cancer patients with these factors should be considered to receive aggressive adjuvant treatment and frequent post-operative follow-up.

**Abbreviations:** ASA = American Society of Anesthesia, CCRT = concurrent chemoradiation therapy, EBL = estimated blood loss, LN = lymph node, LOS = length of hospital stay, PD = pancreaticoduodenectomy, RBC = red blood cell, TMA = tissue microarray.

**Keywords:** ampullary cancer, histopathologic subtype, immunohistochemical expression, very early recurrence

## 1. Introduction

Ampullary cancer is rare and accounts for 0.5% of all gastrointestinal malignancies and 30% of cancers requiring pancreatoduodenectomy (PD).[1,2] The location of ampullary cancer contributes to the easy development of the symptoms or signs; therefore, earlier detection and diagnosis of this cancer than other periampullary cancers is helpful. With improvements in the preoperative evaluation strategy, surgical techniques, and postoperative care, the prognosis of ampullary cancer following surgical resection has improved. However, ampullary cancer has approximately 30% rate of lymph node (LN) metastasis, even in T1 cancer, and a high recurrence rate of up to 50% after surgical resection.[3–6] Additionally, ampullary cancer is histologically known to be a heterogenous disease. Kimura et al reported 2 histologic subtypes of ampullary cancer pancreatobiliary type and intestinal type.[7] The pancreatobiliary type originates from the endothelium of the common ampullary channel, distal pancreatic duct, or distal common bile duct; evolves from an intraepithelial neoplasia. The intestinal type originates from the intestinal epithelium overlying the ampulla and evolves from an adenoma dysplasia sequence of stomach or colon. The pancreatobiliary type has a strong infiltrative tendency, compared with the intestinal type.[8,9] Additionally, LN metastases a representative prognostic factor in ampullary cancer are more frequently detected in the pancreatobiliary type than in the intestinal type.[10,11]

Ampullary cancer has been immunohistochemically classified because of limitations in the accuracy of histopathologic classification.[12] However, the prognostic significance of IHC results is controversial.[9,13]

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*Synopsis: This study is designed to identify the factors for very early recurrence (within 6 months) of ampullary cancer following curative resection and to compare the immunohistochemical expression rate of various antibodies between the two main histologic subtypes of ampullary adenocarcinoma.*

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Investigations on the early recurrence of ampullary cancer following surgical resection are few. In the available studies, early recurrence was defined as that occurring within a year after curative resection.

In this study, we aimed to identify factors associated with very early recurrence of ampullary cancer within 6 months following surgery and compare IHC expression rates of several antibodies between the 2 main histologic subtypes of ampullary adenocarcinoma.

## 2. Methods

### 2.1. Study population and data collection

In this retrospective study, we defined very early recurrence as that detected within 6 months after curative resection. We reviewed medical records of patients diagnosed as ampullary cancer at the National Cancer Center in Korea between January 2002 and August 2014 to assess the impact of various factors on prognosis. Patients were stratified into 2 groups based on whether recurrence after curative resection was early or not. Several factors including characteristics, pathologic results, and surgical outcomes were reviewed. Patient characteristic included sex, age, American Society of Anesthesia (ASA) score, preoperative serum total bilirubin level, preoperative serum preoperative CA 19-9 level, and the need for preoperative biliary drain. Pathologic factors included pancreatic consistency; tumor size; margin status; gross subtype; histologic subtype; IHC staining results; cell differentiation; T stage; and presence/absence of microvascular invasion; perineural invasion; LN metastasis or not, and multiple LN metastases. Surgical outcomes included the need for portal vein resection, estimated blood loss (EBL), operation time, amount of red blood cell (RBC) transfusion, length of hospital stay (LOS), and Clavien–Dindo (C–D) classification.[14] Approval was obtained from the institutional ethical committee (*Institutional Review Board*, National Cancer Center, Korea) before starting the study (NCC2019-0138).

### 2.2. Operation and postoperative management protocol

Surgical techniques and postoperative management protocol were similar for all patients during study period. During PD for periampullary malignancies, we routinely dissected LNs LNs #8, #12, #13, #14, and #17. If the surgeon decided to extend lymphadenectomy, then LNs #15 and #16 were dissected. Indications for RBC transfusion included significant perioperative blood loss, serum hemoglobin concentration <7 g/dL, or serum hemoglobin level of 7 to 10 g/dL, combined with any signs or symptoms of acute bleeding. Patients who recovered after operation and agreed with adjuvant treatment started the treatment on week 5 from the operation day. The chemotherapy regimen was 5-FU (5–15 mg/kg) based. When recurrence occurred, palliative chemotherapy based on capecitabine (2500 mg/m$^2$/day, once a week for 2 weeks and skip on week 3) was administered. Adjuvant concurrent chemoradiation therapy (CCRT) was administered as 5040 cGY in 28 fractions, with 5-FU on the first and last 3 days.

### 2.3. Histopathologic evaluation

Cases were reviewed by a pathologist and the pathologic cancer was re-staged according to the eighth edition of the TNM staging system for ampullary carcinoma issued by the American Joint Committee on Cancer in 2016.[15] Positive margins were macroscopically or microscopically defined as tumor involvement at the resection margins. A margin clearance >0 mm was defined as R0 resection. According to the criteria that used cytologic and architectural features and revised by Albores-Saavedra et al and Adsay et al, cases of ampullary cancer were classified as intestinal or pancreatobiliary.[16,17]

For IHC staining, after screening for representative tumor regions by a pathologist, 2 cores of tumor were sampled from formalin-fixed paraffin-embedded tissue blocks from each patient using a 3.0-mm punch. Tissue microarray (TMA) was constructed using a tissue microarrayer (Quick Ray, UNITMA Co Ltd. Seoul, Korea), and IHC stains using 8 antibodies were performed on the 4-μm sections from TMA blocks. Antibodies were CK7 (clone OV-TL 12/30, 1:300, Dako, Carpinteria, CA), CK20 (clone Ks 20.8, 1:400, Dako), CDX2 (EPR2764Y, 1:50, Cell Marque, Rocklin, CA), MUC1 (clone Ma695, 1:100, Leica Microsystems, Newcastle upon Tyne, UK), MUC2 (clone Ccp58, 1:100, Leica Microsystems), MUC5AC (clone CLH2, 1:200, Leica Microsystems), MUC6 (clone CLH5, 1:200, Leica Microsystems), and S100P (cone EPR6142, 1:4,000. Abcam, Cambridge, UK). IHC staining was performed using Benchmark XT automated immunohistochemistry stainer (Ventana Medical Systems, Tucsan, AZ). Detection was done using the Ventana I-view or Ultraview DAB kit. Sections were stained as follows: sections were deparaffinized and rehydrated in graded alcohol. For heat-induced epitope retrieval, slides were subjected to a CC1 solution (pH 8.4 buffer containing Tris/Borate/EDTA) at 100 °C for 30 to 60 minutes and allowed to cool at room temperature for another 10 minutes. Slides were incubated with 3% hydrogen peroxide for 10 minutes, followed by blocking of endogenous avidin/biotin. After blocking, slides were incubated with the eight antibodies at 42 °C for 32 to 60 minutes. After rinsing with wash buffer, slides were incubated with Universal HRP multimer at 37 °C for 8 minutes. Then, slides with DAB for 10 minutes at room temperature and were finally counterstained with hematoxylin II and a bluing reagent.

Cases that showed >5% tumor cell positivity were considered as positive.[18] The percentage of immunoreactive cells was calculated as the number of immunoreactive cells over the total number of tumor cells established expression of antibody.

### 2.4. Follow-up assessment

Follow-up evaluation included tumor assessment by chest and abdominal–pelvic CT, tumor marker levels, and other laboratory tests. Follow-up data were obtained from medical records or by telephone contact up to December 2017. Patients were followed every month during the first 3 months, every 3 months during the first year, and every 6 months thereafter. Postoperative recurrence was determined based on radiologic image evaluation on CT. The primary endpoint of recurrence of ampullary cancer after PD or PPPD was compared between the very early recurrence and other patients groups. The secondary endpoint was identification of factors indicating very early recurrence. Additionally, we evaluated postoperative outcomes of patients who underwent PD or PPPD. Postoperative morbidities were defined as operation-related complications occurring within 90 days from the operation day.

### 2.5. Statistical analysis

IBM SPSS version 22.0 (IBM Corp., Armonk, NY) was used to analyze data. Kaplan–Meier method was used to analyze overall survival (OS), and log-rank test was used to compare survival rates between the very early recurrence and other patients groups. Baseline characteristics of patients are presented as number and percentage for

categorical variables and as median with range for continuous variables. Wilcoxon rank sum test was used to analyze differences in continuous variables. Pearson chi-square test was used to compare categorical variables. To investigate the combined effects of different variables on very early recurrence of ampullary cancer after curative resection, multivariate analyses were performed using a binary logistic regression model. For all tests, $P$ value $<.05$ was considered significant, corresponding to a 95% confidence interval (CI).

## 3. Results

### 3.1. Patients

Among the 117 patients who underwent curative resection by PD or PPPD for ampullary cancer at the National Cancer Center in Korea between January 2002 and August 2014, patients who underwent other operation in addition to pancreatoduodenectomy or pylorus preserving pancreatoduodenectomy (N=3), patients whose final pathologic diagnosis was not adenocarcinoma (N=11), follow-up loss (N=2), and those in whom pathologic review and/or IHC analysis was not possible (N=8) excluded. Finally, 93 patients were included and allocated to the very early recurrence (N=14) or other patients (N=79) groups. The other patients group included patients with recurrence occurring later than 6 months after curative resection (N=26) and those without recurrence after surgery (N=53). The median duration of follow-up after PD or PPPD was 53 months for all patients.

### 3.2. Comparisons of postoperative prognosis and clinicopathologic factors between the early recurrence and other patients groups

Postoperative recurrence of ampullary cancer occurred in 43% (40/93) patients and was early in 14 (15.1%) patients. Figure 1 shows OS after PD or PPPD for ampullary cancer patients. The respective actuarial 1, 3, and 5-year survival rates were 91.4%, 68.7%, and 56.7% and were significantly lower in the very early recurrence group (71.4%, 14.3%, and 0%) than in the other patients (94.9%, 78.3%, and 66.9%; $P<.001$, log-rank test). There was no significant difference between the groups in terms of sex, median age, ASA score, preoperative serum total bilirubin level, preoperative serum CA 19-9 level, and rate of preoperative biliary drain insertion (Table 1).

**Table 1**

**Characteristics and demographics of the patients.**

| Characteristics | Very early recur (N=14) | Others (N=79) | *P* value |
|---|---|---|---|
| Sex | | | .310 |
| Male | 10 (71.4%) | 45 (57.0%) | |
| Female | 4 (28.6%) | 34 (43.0%) | |
| Age (year) | 66.5±7.2 | 62.0±9.5 | |
| ASA score | | | .542 |
| 1 | 2 (14.3%) | 16 (20.3%) | |
| 2 | 10 (71.4%) | 58 (73.4%) | |
| 3 | 2 (14.3%) | 5 (6.3%) | |
| Preop. T Bil | 2.2±3.8 | 1.4±2.9 | .174 |
| Preop. CA 19-9 | 32.4±698.3 | 18.2±4293.8 | .774 |
| Preop. Biliary Drain | | | .803 |
| - | 5 (35.7%) | 31 (39.2%) | |
| + | 9 (64.3%) | 48 (60.8%) | |

ASA = American Society of Anesthesia, CA 19-9 = carbohydrate antigen 19-9, Preop. = preoperative, Recur = recurrence, T. bil = total bilirubin.

### 3.3. Histopathologic and operative results

Compared with the other patients group, the very early recurrence group had larger tumors; more frequent pancreatobiliary subtype;

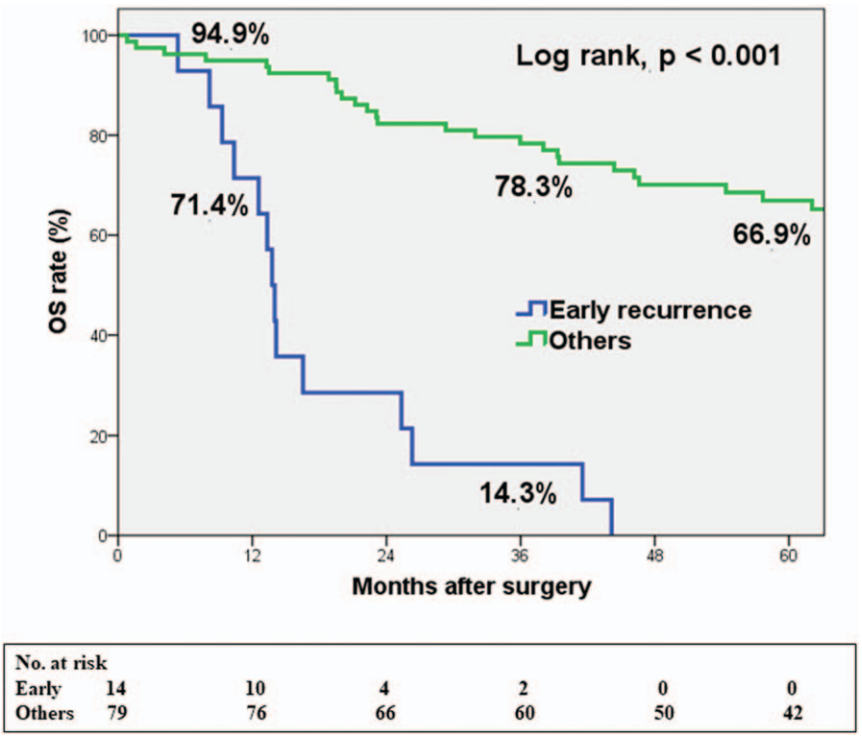


**Figure 1.** Comparison of the overall survival in patients with ampullary cancer after pancreatoduodenectomy between the very early recurrence group and the others group.

**Table 2**

**The factors associated with postoperative outcomes following pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy.**

| Characteristics | Very early recur (N = 14) | Others (N = 79) | *P* value |
|---|---|---|---|
| Pancreatic consistency | | | .628 |
| Soft | 9 (69.2%) | 52 (75.4%) | |
| Frim | 2 (15.4%) | 12 (17.4%) | |
| Hard | 2 (15.4%) | 5 (7.2%) | |
| Tumor size (cm) | | | .046 |
| ≤3.0 | 9 (64.3%) | 68 (86.1%) | |
| >3.0 | 5 (35.7%) | 11 (13.9%) | |
| Margin status | | | .672 |
| R0 | 14 (100%) | 78 (98.7%) | |
| R1 | 0 | 1 (1.3%) | |
| Gross type | | | .280 |
| Non-ulcerative | 10 (71.4%) | 66 (83.5%) | |
| Ulcerative | 4 (28.6%) | 13 (16.5%) | |
| Histologic type | | | .001 |
| Pancreatobiliary | 10 (71.4%) | 21 (26.6%) | |
| Intestinal | 4 (28.6%) | 58 (73.4%) | |
| Histologic subtype II | | | .080 |
| Periampullary | 2 (14.3%) | 9 (11.4%) | |
| Ampullary | 7 (50.0%) | 16 (20.3%) | |
| Ampullary-ductal | 3 (21.4%) | 22 (27.8%) | |
| Intraampullary | 2 (14.3%) | 32 (40.5%) | |
| Cell differentiation | | | .036 |
| WD | 0 | 19 (24.1%) | |
| MD | 5 (35.7%) | 34 (43.0%) | |
| PD | 9 (64.3%) | 26 (32.9%) | |
| Microvascular invasion | | | .004 |
| N | 10 (71.4%) | 75 (94.9%) | |
| Y | 4 (28.6%) | 4 (5.1%) | |
| Perineural invasion | | | .004 |
| N | 5 (35.7%) | 59 (74.7%) | |
| Y | 9 (64.3%) | 20 (25.3%) | |
| T stage | | | .001 |
| 1 | 2 (14.3%) | 39 (49.4%) | |
| 2 | 1 (7.1%) | 18 (22.8%) | |
| 3 | 11 (78.6%) | 22 (27.8%) | |
| N stage | | | <.001 |
| 0 | 1 (7.1%) | 50 (63.3%) | |
| 1 | 4 (28.6%) | 26 (32.9%) | |
| 2 | 9 (64.3%) | 3 (3.8%) | |
| No. LN metastasis | | | <.001 |
| <4 | 5 (35.7%) | 76 (96.2%) | |
| ≥4 | 9 (64.3%) | 3 (3.8%) | |
| CK7 | | | .326 |
| − | 2 (14.3%) | 21 (26.6%) | |
| + | 12 (85.7%) | 58 (73.4%) | |
| CK20 | | | .061 |
| − | 10 (71.4%) | 35 (44.3%) | |
| + | 4 (28.6%) | 44 (55.7%) | |
| CDX2 | | | .061 |
| − | 7 (50.0%) | 20 (25.3%) | |
| + | 7 (50.0%) | 59 (74.7%) | |
| MUC1 | | | .003 |
| − | 1 (7.1%) | 39 (49.4%) | |
| + | 13 (92.9%) | 40 (50.6%) | |
| MUC2 | | | .547 |
| − | 14 (100%) | 77 (97.5%) | |
| + | 0 | 2 (2.5%) | |
| MUC5AC | | | .570 |
| − | 13 (92.9%) | 76 (96.2%) | |
| + | 1 (7.1%) | 3 (3.8%) | |
| MUC6 | | | .333 |
| − | 14 (100%) | 74 (93.7%) | |
| + | 0 | 5 (6.3%) | |
| S100P | | | .971 |
| − | 2 (14.3%) | 11 (13.9%) | |
| + | 12 (85.7%) | 68 (86.1%) | |

LN = lymph node, MD = moderate differentiated, No. = number, PD = poor differentiated, recur = recurrence, WD = well differentiated.

and more cases with poor cell differentiation, microvascular invasion, perineural invasion, advanced T stage, and multiple LN metastases. Among various antibodies applied for IHC staining, only MUC1 showed a significant difference in the staining rate between the groups; MUC1 positivity was more common in the very early recurrence group than in the other patients group (Table 2). Operative outcomes were comparable between 2 groups (Table 3).

### 3.4. Factors associated with very early recurrence

Univariate analysis showed that large tumor size (>3 cm), poor cell differentiation, advanced T stage, LN metastasis, multiple LN metastases, microvascular invasion, perineural invasion, pancreatobiliary subtype, and MUC1 positivity were associated with very early recurrence of ampullary cancer after PD or PPPD. Among these, larger tumor size, LN metastasis, multiple LN metastases, and pancreato-biliary subtype were independent risk factors for very early recurrence of ampullary cancer following PD or PPPD (Table 4).

### 3.5. Patterns of recurrence

Of the 40 patients who developed recurrence after surgical resection, 11 (27.5%) had locoregional recurrence and 29 (72.5%) had distant recurrence. The most common organ for metastasis was the liver (N = 17), followed by the lungs (N = 5), bone (N = 3), distant peritoneum (N = 2) and others (cervical LN

**Table 3**

**Operative results following pancreaticoduodenectomy or pylorus-preserving pancreatoduodenectomy.**

| Characteristics | Very early recur (N = 14) | Others (N = 79) | *P* value |
|---|---|---|---|
| PV resection | | | .672 |
| N | 14 (100%) | 78 (98.7%) | |
| Y | 0 | 1 (1.3%) | |
| EBL (mL) | 525 ± 529.3 | 500 ± 477.0 | .602 |
| Op. time (min.) | 365 ± 58.2 | 346 ± 80.3 | .668 |
| Intraop. RBC Tf. (pack) | 0 ± 0.9 | 0 ± 0.7 | .426 |
| Postop. RBC Tf. (pack) | 0 ± 1.3 | 0 ± 2.1 | .770 |
| LOS (day) | 22 ± 9.6 | 19 ± 13.4 | .839 |
| Clavien-Dindo classification | | | .067 |
| 0–2 | 8 (57.1%) | 63 (79.7%) | |
| 3–4 | 6 (42.9%) | 16 (20.3%) | |

EBL = estimated blood loss, Intraop. = intraoperative, LOS = length of hospital stay, Op. = operation, Postop. = postoperative, PV = portal vein, recur = recurrence, RBC = red blood cell, Tf. = transfusion.

**Table 4**

**Multivariate analysis of the factors for very early recurrence following surgery.**

| Characteristics | *P* value | OR | 95.0% CI | |
|---|---|---|---|---|
| | | | Min. | Max. |
| Tumor size > 3 cm | .042 | 71.215 | 1.175 | 4317.636 |
| Poor differentiation | .480 | 2.839 | 0.157 | 51.210 |
| T stage ≥3 | .152 | 7.884 | 0.468 | 132.883 |
| LN metastasis | .017 | 47.746 | 2.010 | 1134.093 |
| Microvascular invasion | .480 | 2.807 | 0.160 | 49.108 |
| Perineural invasion | .132 | 8.423 | 0.528 | 134.428 |
| Pancreatobiliary type | .041 | 28.150 | 1.140 | 694.951 |
| MUC1 + | .997 | | | |
| Metastatic node ≥4 | .010 | 32.822 | 2.269 | 474.695 |

CI = confidence interval, LN = lymph node, OR = odds ratio.

or distal ileum). There was no significant difference in the rate of recurred site between the very early recurrence group and the other patients group of patients in whom the recurrence occurred after 6 months of operation (Table 5).

### 3.6. Comparison between pancreatobiliary and intestinal subtypes

There were 31 patients with the pancreatobiliary subtype and 49 with the intestinal subtype. Using the same factors applied to aforementioned comparisons between the very early recurrence group and the other patients group, patients with the pancreatobiliary subtype had more cases of advanced T stage (51.6% vs 26.5%, $P = .020$) and multiple LN metastases (22.6% vs 6.1%, $P = .030$) than hose with the intestinal subtype.

For IHC staining, compared with patients with intestinal subtype, those with pancreatobiliary subtype had more frequent positive staining for CK7, MUC1, and S100P; less frequent CK20 positivity and CDX2 positivity; and similar staining rates for MUC2, MUC5AC, and MUC 6 (Table 6).

## 4. Discussion

Ampullary cancer is rare; therefore, studies on ampullary cancer had not been active and most were small and/or retrospective studies.[19] Some studies have investigated prognostic factors for OS and/or disease-free survival (DFS) in patients with ampullary cancer after surgery. However, studies about early recurrence of ampullary cancer after surgery has are rare and defined early recurrence as that occurring within 1 year after surgical resection.

And they failed to show the significant difference of IHC staining between early recurrence group and control group. In addition, sometimes biliary-pancreas surgeons can experience the very early recurrence without any significant cause in patients with ampullary cancer following curative resection. Through this study, therefore, we tried to identify the factors of very early recurrence through this study. Recurrence of ampullary cancer occurred within 5 years after surgery in 43.5% of patients, and the patients with very early recurrence showed significantly worse survival rate than other patients. Therefore, identification of factors for very early recurrence may help to improve the prognosis of patients with ampullary cancer.

In this study, large tumor, LN metastasis, and pancreatobiliary subtype significantly increased chances for very early recurrence in patients with ampullary cancer after PD or PPPD. Tumor size and LN metastasis are directly associated with advanced ampullary cancer, and advanced stage of ampullary cancer is

**Table 5**

**Recurrence pattern following pancreaticoduodenectomy or pylorus-preserving pancreatoduodenectomy.**

| | Early (N = 14) | Late (N = 26) | *P* value |
|---|---|---|---|
| Recurred organ | | | |
| Local recurrence | 4 (28.6%) | 7(26.9%) | .911 |
| Liver metastasis | 8 (57.1%) | 9 (34.6%) | .169 |
| Lung metastasis | 1 (7.1%) | 4 (15.4%) | .452 |
| Bone metastasis | 0 | 3 (11.5%) | .186 |
| Peritoneal seeding | 0 | 2 (7.7%) | .287 |
| Other metastases | 1 (7.1%) | 1 (3.8%) | .648 |

**Table 6**

**The results of immunohistochemistry staining according to the type of ampullary cancer.**

| Characteristics | PB (N = 31) | Intest. (N = 62) | *P* value |
|---|---|---|---|
| CK7 | | | .017 |
| − | 3 (9.7%) | 20 (32.3%) | |
| + | 28 (90.3%) | 42 (67.7%) | |
| CK20 | | | <.001 |
| − | 27 (87.1%) | 18 (29.0%) | |
| + | 4 (12.9%) | 44 (71.0%) | |
| CDX2 | | | <.001 |
| − | 19 (61.3%) | 8 (12.9%) | |
| + | 12 (38.7%) | 54 (87.1%) | |
| MUC1 | | | .001 |
| − | 6 (19.4%) | 34 (54.8%) | |
| + | 25 (80.6%) | 28 (45.2%) | |
| MUC2 | | | .312 |
| − | 31 (100%) | 60 (96.8%) | |
| + | 0 | 2 (3.2%) | |
| MUC5AC | | | .718 |
| − | 30 (96.8%) | 59 (95.2%) | |
| + | 1 (3.2%) | 3 (4.8%) | |
| MUC6 | | | .745 |
| − | 29 (93.5%) | 59 (95.2%) | |
| + | 2 (6.5%) | 3 (4.8%) | |
| S100P | | | .034 |
| − | 1 (3.2%) | 12 (19.4%) | |
| + | 30 (96.8%) | 50 (80.6%) | |

Intest. = intestinal, PB = pancreatobiliary.

associated with poor prognosis. Recently, the Mayo clinic reported that advanced stage was an independent predictor of OS in patients with ampullary cancer after surgery, although they failed to show the effect of advanced stage on postoperative recurrence.[20] Dogeas et al reported the association between tumor size and nodal metastasis and recommended lymphadenectomy for periampullary cancer, especially in patients with large tumor (>1 cm).[21] Although controversial, histologic subtype has been known as an important prognostic factor for ampullary cancer. In a meta-analysis by Zhou et al, the pancreatobiliary subtype predicted a worse OS and DFS.[22] In our analysis, large tumor and LN metastasis were more common in the pancreatobiliary type than in the intestinal type. These results implied that compared with other types, pancreatobiliary type was more aggressive and a worse prognostic subtype of ampullary cancer.

Although there was no significant difference on recurrence pattern between the very early recurrence and other patients groups, among 11 patients occurring local recurrence 6 patients showed LN metastases at left side of SMA (each 3 patients in both groups). As Kim et al reported, therefore, careful LN dissection around the SMA should be considered for ampullary cancers.[23]

Based on literature and our experience, we selected antibodies (CK7, CK20, CDX20, MUC1, MUC2, MUC5AC, MUC6, and S100P) for IHC.[24–33] However, IHC staining result were not independently associated with very early recurrence of ampullary cancer after surgical resection. This result was supported by previous studies, which reported IHC staining was not associated with postoperative prognosis.[34,35] However, IHC staining were associated with the histologic subtype of ampullary cancer. In particular, CK7, MUC1, and S100P were common in pancreatobiliary type, whereas CK20 and CDX2 were common in the intestinal type. Therefore, although IHC staining cannot be used as a prognostic predictor, it may be helpful distinguishing the ampullary cancer subtype that has a prognostic significance for very early recurrence after surgery

Recently, ampullary cancer has been considered as heterogenous disease, and genomic studies for ampullary cancer has been reported steadily; accordingly, a precise therapeutic strategy, such as targeted therapy, is believed to overcome the limitation of present therapeutic regimen for ampullary cancer.[36–38]

Hechtman et al argued that overexpression of ERBB2, a potential target for anti HER2 therapy occurred in 13% of all ampullary carcinomas. However, the studies for target therapy have been mostly small-scale and they could not show any definite effect of target therapy on postoperative prognosis in patients with ampullary cancer. The study of target therapy is now in its beginning stage and has a long way to go. It is true that the weapons that we can use in practice to reduce the very early recurrence of ampullary cancer are limited, such as chemotherapy, chemoradiation therapy, and photodynamic therapy. However, the active use of these weapons to the high-risk patients for very early recurrence, even if patients with early stage cancer, may be helpful to reduce very early recurrence. The IHC staining result in this study showed that the positive staining rate of CK7, MUC1, and S100P which are known as antibodies showing high positive rates in pancreatic cancer were significantly higher in patients with pancreatobiliary type of ampullary cancer than others. Therefore, the adjuvant therapy which is recommended to pancreatic cancer may be helpful to reduce very early recurrence in patients with pancreatobiliary type of ampullary cancer.[39] The effect of these adjuvant therapy have to be validated through large scale study including multi-institutional study or randomized trial.

This study had some limitations. First, as with all retrospective studies, there may have been a selection bias regarding the diagnosis and treatment of patients with ampullary cancer. Missing data points according to the specific histologic subtype were also inherent flaws of its retrospective design. Additionally, the number of cases was small despite a study period of >10 years; this reflected the fact that patients with resectable ampullary cancer were not common and are rarely enrolled in a single institution. The effects of IHC staining results on very early recurrence were analyzed separately by score, in the early stages of analysis, but it did not show any particular results. Due to the small number of people studied, in addition, we judged that it would be too difficult to apply statistical analysis. Therefore, the results of IHC staining were simplified for analysis. If sufficient numbers of subjects were obtained through multi-organ studies, it would be appropriate to conduct a statistical analysis based on the scores of immunochemical dyeing results.

In conclusion, we identified large tumor, LN metastasis, and pancreatobiliary type as independent risk factors for very early recurrence of ampullary cancer following curative resection. Therefore, ampullary cancer patients with these factors should receive proactive adjuvant treatment and more frequent follow-up. Additionally, different strategies of adjuvant therapy may be helpful to improve outcomes of the different histologic tumor subtypes.

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