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# Identification of patients at high risk for recurrence in carcinoma of the ampulla of Vater: Analysis in 460 patients

Masato Narita[1,2] | Etsuro Hatano[3] | Koji Kitamura[4] | Ken Fukumitsu[5] | Hirohisa Kitagawa[6] | Yuhei Hamaguchi[7] | Takefumi Yazawa[8] | Hiroaki Terajima[9] | Kazuhiko Kitaguchi[10] | Toshihiko Hata[11] | on behalf of the Kyoto University Hepato-Biliary Pancreatic surgery Study Group (KUHBPS)

[1]Department of Surgery, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

[2]Department of Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

[3]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[4]Department of Surgery, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

[5]Department of Surgery, Kyoto Katsura Hospital, Kyoto, Japan

[6]Department of Surgery, Kurashiki Central Hospital, Kurashiki, Japan

[7]Department of Surgery, Japanese Red Cross Osaka Hospital, Osaka, Japan

[8]Department of Surgery, Shiga General Hospital, Shiga, Japan

[9]Department of Surgery, Kitano Hospital, Osaka, Japan

[10]Department of Surgery, Japanese Red Cross Otsu Hospital, Otsu, Japan

[11]Department of Surgery, Kobe City Medical Center West Hospital, Kobe, Japan

**Correspondence**
Etsuro Hatano, Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
Email: etsu@kuhp.kyoto-u.ac.jp

## Abstract

**Aim:** Carcinoma of the ampulla of Vater (CAV) shows a favorable prognosis compared to that with the other periampullary tumors, while some cases have a poor prognosis. The aims of the present study are to clarify the clinicopathological factors associated with poor recurrence-free survival (RFS) in patients with CAV after curative resection and to validate the usefulness of adjuvant chemotherapy (AC).

**Patients:** The study design is a multicenter retrospective cohort study. Patients with CAV who underwent pancreaticoduodenectomy between January 2008 and December 2020 at 26 hospitals were analyzed. The 30 clinicopathological factors were evaluated. A propensity score matching (PSM) was used to compare between patients with and without AC.

**Results:** Finally, 460 patients were analyzed. Median duration of follow-up was 47.2 months. Twenty-one prognostic factors associated with poor RFS were identified by univariate analysis. In multivariate analysis, aged ≥71, tumor diameter ≥12 mm, pT2 or higher stage (pT≥2), portal vein invasion (PV+), venous invasion(V+), and node positive disease (pN+) were independent prognostic factors for poor RFS. Out of 80 patients who received AC, 63 patients were assigned to analysis for PSM. The results showed no beneficial effect of AC on RFS. The preoperative factors potentially predicting pT≥2, V+, and/or N+ were at least one of following; (1) CA19-9 > 37 IU/mL, (2) ulcerative or mixed type appearance, (3) except for well-differentiated tumor, or (4) except for intestinal subtype of histology.

**Conclusions:** Aged ≥71, tumor diameter ≥12 mm, pT≥2, PV+, V+, and pN+ were independent prognostic factors for poor RFS in patients with CAV. An additional therapeutic strategy may be desirable in CAV patients at high risk for recurrence.

KEYWORDS

adjuvant chemotherapy, ampullary cancer, neoadjuvant chemotherapy, overall survival, prognosis

## 1 | INTRODUCTION

Carcinoma of the ampulla of Vater (CAV) shows a favorable prognosis compared to the other periampullary tumors, while some cases have a poor prognosis. Multiplicity of prognosis in CAV patients may be due to the heterogeneity of tumor biology, morphological diversity, and genetic alteration in CAV. To date, various clinicopathological factors associated with poor prognosis in patients with CAV have been determined, including tumor marker, nodal involvement, pathological T stage (pT), lymphovascular invasion, perineural invasion, histopathological subtypes, and adjuvant chemotherapy (AC).[1–5] However, definitive data are still lacking since most studies were conducted in a small number of patients at a single institution. Although there have been the three largest multicenter series reporting prognostic factors in patients with CAV, many missing data, particularly in histological subtype, precluded to obtain the decisive conclusions.[6–8] Furthermore, the role of AC in this setting remains a controversial subject.[6,7,9] Thus, no effective therapeutic strategy for CAV patients with poor prognosis has been established so far. The aims of the present study are to clarify the clinicopathological factors associated with poor recurrence-free survival (RFS) in patients with CAV after curative resection and to validate the usefulness of AC in a multicenter, retrospective cohort study.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design

This was a retrospective multicenter, observational cohort study performed at 26 hospitals belonging to Kyoto University Hepato-Biliary-Pancreatic surgery Study Group (KUHBPS). This study was approved by the central institutional review board for multi-institutional retrospective research in Kyoto Medical Center (approval number; 21–071).

### 2.2 | Study population

The study population of the present study met both of the following criteria: (1) patients histologically diagnosed with CAV, and (2) patients who underwent pancreaticoduodenectomy (PD) for curative intent at the participating hospital between January 2008 and December 2022. The main exclusion criteria were patients with metastatic disease, those with peritoneal cytology positive during surgery, those who underwent resection with macroscopic residual tumor (R2), those with CAV containing a component of neuroendocrine cancer, and those who died of postoperative complications. The patient who met at least one of the exclusion criteria were excluded.

### 2.3 | Study outcome

The primary outcome was recurrence-free survival (RFS).

In the present study, following issues were evaluated:

1. The clinicopathological factors associated with poor RFS and overall survival (OS) was determined.
2. The role of postoperative AC was evaluated by propensity score matching (PSM).
3. Potential candidates for neoadjuvant chemotherapy were identified.

### 2.4 | Surgical procedures and patient management

PD was performed as either pylorus-preserving, subtotal stomach-preserving, or classical PD. Regional lymphadenectomy was performed, and its extent was according to the condition of the primary disease. The reconstruction procedure was performed by either pancreaticojejunostomy (PJ) or invaginated pancreaticogastrostomy (PG) according to the surgeon's preferences.

### 2.5 | Definitions

Prognostic nutrition index (PNI) was calculated as $10 \times$albumin (g/dL) $+ 0.005 \times$total lymphocyte count (no./mm$^3$).[10]

Postoperative pancreatic fistula (POPF) was graded according to the International Study Group on Pancreatic Fistula classification. The clinically relevant (CR)-POPF was defined as POPF of grade B or C.[11]

Postoperative morbidity was graded according to the Clavien–Dindo classification.[12] Major complication was defined as grade III or higher.[13]

Pathological findings except for histological subtype were documented according to the General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract (7th edition).[14]

Histological subtypes were classified as the intestinal type, pancreatobiliary type, mixed type, or unclassified according to the WHO Classification of Tumors of the Digestive System (5th edition).[15]

RFS was defined as the duration from the date of curative surgery to diagnosis of recurrence. RFS is censored on the last day of survival confirmation for surviving patients without recurrence.

Recurrence was confirmed by imaging examination.

### 2.6 | Statistical analysis

Quantitative variables are expressed as median (IQR). Qualitative variables are expressed as numerical values (percentages). The comparative analysis for the continuous variables of two groups

was performed using the Student's *t*-test. A comparison between groups with categorical variables was made using the Pearson's chi-square test or Fischer's exact test when appropriate. The cut-off value of continuous variables to predict recurrence was identified by receiver-operating characteristic curve (ROC) analysis and determined using the maximum Youden index method. The Kaplan–Meier method was used to calculate the cumulative incidence of recurrence, and a log-rank test was used to test for a significant difference in the comparison between the two groups. A multivariate Cox proportional hazard model was used to evaluate the effect of each parameter on RFS and OS. The variables with a $p$ value <0.10 in the univariate analysis were included in the multivariate analysis. A propensity score matching (PSM) was conducted to adjust for selection bias. A propensity score for each patient was estimated using a logistic regression model with AC as the dependent variable. Confounding variables were selected based on the results of univariate analysis to determine factors associated with poor RFS. After the propensity scores were estimated, one-to-one nearest neighbor matching was performed using a caliper set at 0.2.

A logistic regression analysis was performed to identify the variables predicting each prognostic factor. $p < 0.05$ was considered statistically significant. As the statistical analysis software, JMP (version 14.0.0, SAS Institute Inc.) was used.

## 3 | RESULTS

### 3.1 | Patient baseline characteristics, intra- and postoperative outcomes, and pathological data

Out of 476 patients registered, 16 patients were excluded from the analysis (Figure 1). In 460 patients analyzed, 274 patients were male and 186 were female; median age was 72 (64–77) years. The details of patients' baseline characteristics were shown in Table 1. Preoperative biliary drainage was required in more than half of the patients. Table 2 showed intra- and postoperative outcomes. AC was administered in 80 (17.4%) patients. The details of pathological findings were shown in Table 3. About three-quarters of patients had protruded type of tumor. Well-differentiated tumor was seen in more than half of the patients. Regarding histological subtypes, intestinal subtype was the most frequently seen in this population. Tumor depth of duodenal invasion or higher stage (pT≥2) was observed in 270 (58.7%) patients. Nodal involvement (N+) was 33.5% of this population. Ten patients had microscopic residual tumor (R1) resection.

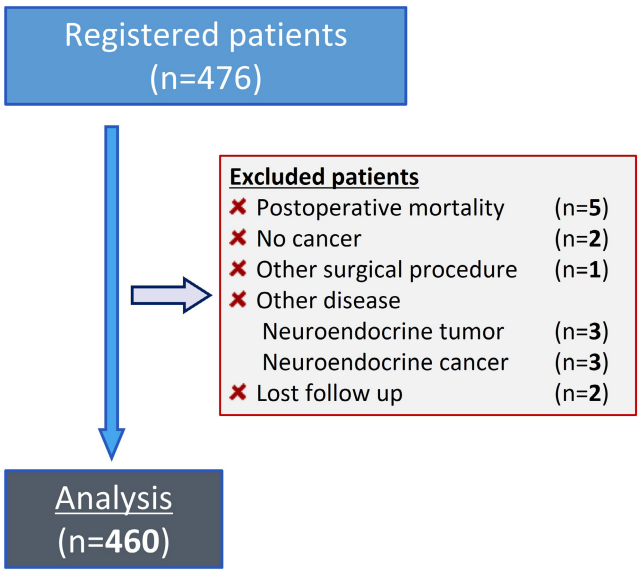


FIGURE 1 A flow diagram of the present study.

### 3.2 | Primary outcome

The 1-year, 2-year, 3-year, 4-year, and 5-year RFS rates were 82.5%, 72.4%, 70.3%, 67.5%, and 66.8%, respectively. One hundred forty-three patients (31.1%) developed tumor recurrence during median duration of follow-up at 47.2 months, ranging from 2.5 to 164.9 months. Of 143 patients with tumor recurrence, the median duration between the date of documented recurrence and the date of the most recently performed imaging before being diagnosed with recurrence was 3.7 months (ranging from 0.2 to 36.2 months), and 21 patients had more than 6 months interval. Tumor recurrence developed within 6 months, 1 year, and 2 years after curative resection in

TABLE 1 Patients' baseline characteristics.

| | Patients, *n* (%) or median (IQR) *N* = 460 |
|---|---|
| Male/Female | 274/186 |
| Age at operation | 72 (64–77) |
| Preoperative BMI[a] | 21.9 (19.9–24.1) |
| Patients with DM | 67 (14.6%) |
| Requiring preoperative biliary drainage | 266 (57.8%) |
| External biliary drainage | 78 |
| Internal biliary drainage | 191 |
| Preoperative laboratory data | |
| Albumin (g/dL) | 3.8 (3.5–4.1) |
| HbA1c (%)[b] | 5.7 (5.4–6.3) |
| Total lymphatic count (/μL)[c] | 1520 (1200–1934) |
| Tumor marker | |
| CEA (ng/mL)[d] | 2.5 (1.7–3.7) |
| CA19-9 (U/mL)[e] | 24.9 (9–56.9) |
| Preoperative chemotherapy | 3 (0.7%) |

Abbreviations: BMI, Body mass index; DM, Diabetes mellitus; IQR, Interquartile range.

[a]BMI data missing for 1 patient.

[b]HbA1c data missing for 125 patients.

[c]Total lymphatic count data missing for 9 patients.

[d]CEA data missing for 4 patients.

[e]CA19-9 data missing for 4 patients.

**TABLE 2** Intra- and postoperative outcomes.

| | Patients, *n* (%) or median (IQR) *N* = 460 |
|---|---|
| Intraoperative outcomes | |
| Surgical procedure | |
| PD | 51 |
| Sub-stomach preserving PD | 295 |
| Pylorus preserving PD | 114 |
| Reconstruction procedure | |
| Modified Child | 430 |
| Whipple | 1 |
| Invaginated pancreatico-gastrostomy | 29 |
| Duration of surgery (min) | 454 (387–533) |
| Amount of blood loss (mL) | 621 (389–1033) |
| Requiring intraoperative transfusion | 69 (9.1%) |
| Postoperative outcomes | |
| Clinically relevant pancreatic fistula | 164 (25.6%) |
| Major complication[a] | 116 (25.2%) |
| Adjuvant chemotherapy | 80 (17.4%) |

Abbreviation: PD, pancreaticoduodenectomy.

[a]Major complication indicates the complication graded as III or higher according to Clavien–Dindo classification.

38 patients (26.6%), 79 patients (55.2%), and 122 patients (85.3%), respectively. Liver was the most frequent site of recurrence (66 patients, 45.8%), followed by lymph nodes (52 patients, 36.1%) and lung (36 patients, 25%). Recurrence at multiple sites was found in 40 patients.

Five-year overall survival (OS) rate for all patients was 67.8% and median survival time (MST) was 144.4 months. On the other hand, 5-year OS rate for patients with tumor recurrence was 24.0% and MST was 31.7 months, which was significantly worse compared to those without recurrence (5-year survival rate; 86.0%, MST; 153.5 months, $p < 0.001$).

## 3.3 | Determination of risk factors associated with poor RFS in all study populations

Univariate analysis on 30 clinicopathological factors including sex, age, BMI, diabetes mellitus, CEA, CA19-9, Albumin, total lymphocyte count (TLC), Neutrophil count (NP), PNI, NP/TLC ratio, preoperative biliary drainage, duration of surgery, amount of blood loss, transfusion, CR-POPF, major complication, gross appearance of tumor, tumor differentiation, histological subtypes, maximum diameter of the tumor, pT-stage, portal vein invasion (PV+), microscopic lymphatic invasion (Ly+), microscopic venous invasion (V+), microscopic perineural invasion (Pn+), INF, nodal involvement (N+), R1, and AC was performed. The results of multivariate analysis performing on all significant variables showed that aged ≥71, maximum diameter of the tumor ≥12 mm, pT ≥2, V+, and N+ were independent prognostic factors for poor RFS (Table 4).

**TABLE 3** Pathological data.

| | Patients, *n* (%) or median (IQR) *N* = 460 |
|---|---|
| Maximum diameter of the tumor (mm) | 18 (13–25) |
| Gross appearance of the tumor | |
| Protruded | 336 |
| Ulcerative | 56 |
| Mixed | 58 |
| Others | 10 |
| Tumor differentiation | |
| wel | 265 |
| mod | 155 |
| por | 26 |
| Others | 14 |
| Histological subtypes[a] | |
| Intestinal type | 215 |
| Pancreatobiliary type | 166 |
| Mixed | 74 |
| Unclassified | 2 |
| T-factor | |
| pTis | 26 |
| pT1a (M) | 68 |
| pT1a (OD) | 42 |
| pT1b (Du) | 54 |
| pT2 (Du) | 126 |
| pT3a (Panc) | 87 |
| pT3b (Panc) | 50 |
| pT4 | 7 |
| Portal vein invasion | 3 |
| INF b/c | 330 (71.7%) |
| Microscopic lymphatic invasion (Ly+) | 165 (35.9%) |
| Microscopic venous invasion (V+) | 148 (32.2%) |
| Microscopic perineural invasion (Pn+)[b] | 96 (20.9%) |
| Node positive disease (N+) | 154 (33.5%) |
| Microscopic residual tumor (R1) | 10 |

Abbreviations: mod, moderately differentiated type; por, poorly differentiated type; PD, pancreaticoduodenectomy; wel, well-differentiated type.

[a]Histological subtype data missing for 3 patients.

[b]Microscopic perineural invasion data missing for three patients.

## 3.4 | Determination of risk factors associated with poor OS in all study populations

The univariate analysis on 30 clinicopathological factors showed that factors included aged ≥71, BMI < 21 kg/m2, CA19-9 > 37 U/mL, Alb<4.0 g/dL, PNI < 45.7, preoperative biliary drainage, duration of surgery ≥502 min, amount of blood loss during surgery ≥522 mL, intraoperative transfusion, AC, gross appearance of the tumor, tumor differentiation, histological subtype, maximum diameter of the tumor ≥12 mm, pT ≥2,

PV+, Ly+, V+, Pn+, R1, and N+ were associated with shorter OS. A multivariate analysis showed that aged ≥71, CA19-9 > 37 U/mL, tumor differentiation except for well-differentiated tumor, INF a, V+, and N+ were independent prognostic factors associated with shorter OS (Table 5).

### 3.5 | Determination of risk factors associated with poor RFS in 380 patients without AC

Univariate analysis on 30 clinicopathological factors, which were described above, was performed in 380 patients who did not receive AC. The results of multivariate analysis performing on all significant variables showed that aged ≥71 (hazard ratio [HR]; 1.95, $p = 0.007$, 95% CI; 1.19–3.25), pT ≥2 (HR; 7.25, $p < 0.001$, 95% CI; 3.15–19.1), PV+ (HR; 6.07, $p < 0.029$, 95% CI; 1.23–22.7), INF b or c (HR; 0.36, $p < 0.012$, 95% CI; 0.17–0.79), V+ (HR; 1.78, $p = 0.015$, 95% CI; 1.12–2.87), and N+ (HR; 3.10, $p < 0.001$, 95% CI; 1.89–5.14) were independent prognostic factors for poor RFS.

### 3.6 | A subgroup analysis to evaluate the clinical effects of AC in the limited patients with poor RFS and OS

The Kaplan–Meier survival analysis was performed in the limited patients with pT ≥2, V+, N+ in terms of RFS and OS to evaluate the clinical effects of AC (Figure 2A–F). The log rank test showed no difference in RFS or OS between the patients with and without AC in all three prognostic factors.

### 3.7 | A propensity score matching to evaluate the efficacy of AC for CAV

AC was administrated in 80 patients with tegafur-uracil in 1, S-1 in 47, gemcitabine in 27, gemcitabine/cisplatin (GC) combination therapy in two, and gemcitabine/S-1 (GS) combination therapy in three patients. Duration of administration of chemotherapy was 3 months

**TABLE 4** Multivariate analysis to determine the clinicopathological factors associated with poor RFS in all study populations.

| Factors associated with shorter RFS on univariate analysis | Recurrence-free MST (months) | Hazard ratio | *p* Value | 95% CI |
|---|---|---|---|---|
| Aged ≥71 | – | 1.84 | 0.003 | 1.22–2.79 |
| BMI < 21 kg/m2 | – | 1.03 | 0.87 | 0.71–1.50 |
| CEA > 5 ng/mL | – | 1.14 | 0.61 | 0.68–1.86 |
| CA19-9 > 37 U/mL | 43.9 | 1.28 | 0.24 | 0.85–1.93 |
| Alb <4.0 g/dL | – | 1.12 | 0.68 | 0.65–1.90 |
| PNI[a] < 45.7 | 43.9 | 1.18 | 0.49 | 0.74–1.94 |
| Preoperative biliary drainage | – | 0.98 | 0.94 | 0.64–1.55 |
| Amount of blood loss ≥522 mL | – | 1.00 | 1.00 | 0.66–1.53 |
| Intraoperative transfusion | – | 1.03 | 0.91 | 0.62–1.68 |
| Adjuvant chemotherapy | 35.6 | 0.82 | 0.36 | 0.53–1.25 |
| Gross appearance; ulcerative and mixed type | – | 1.23 | 0.30 | 0.83–1.79 |
| Maximum diameter of the tumor ≥12 mm | – | 2.04 | 0.034 | 1.05–4.47 |
| Tumor differentiation; except for well-differentiated tumor | – | 1.01 | 0.97 | 0.69–1.50 |
| Histological subtypes; except for intestinal type | – | 1.38 | 0.11 | 0.93–2.08 |
| T-stage; pT2 or more | 42.4 | 4.78 | <0.001 | 2.42–10.3 |
| Portal vein invasion | 6.0 | 5.93 | 0.027 | 1.26–20.6 |
| INF b/c | – | 0.59 | 0.17 | 0.30–1.27 |
| Ly+ | 21.8 | 1.17 | 0.47 | 0.77–1.82 |
| V+ | 21.9 | 1.62 | 0.025 | 1.06–2.49 |
| Pn+ | 25.8 | 0.81 | 0.33 | 0.52–1.24 |
| N+ | 18.1 | 3.05 | <0.001 | 1.94–4.85 |
| R1 | 12.0 | 0.85 | 0.72 | 0.33–1.90 |

Abbreviations: Alb, serum albumin level; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Ly. microscopic lymphatic invasion; MST, median survival time; N, nodal involvement; Pn, microscopic perineural invasion; PNI, prognostic nutrition index; R1, microscopic residual tumor; V, microscopic venous invasion.

[a]PNI was calculated as 10 × albumin (g/dL) + 0.005 × total lymphocyte count (no./mm$^3$).

**TABLE 5** Multivariate analysis to determine the clinicopathological factors associated with poor OS in all study populations.

| Factors associated with shorter OS on univariate analysis | Overall MST (months) | Hazard ratio | *p* Value | 95% CI |
|---|---|---|---|---|
| Aged ≥71 | 89.9 | 1.82 | 0.003 | 1.22–2.74 |
| BMI < 21 kg/m2 | 119.1 | 1.14 | 0.50 | 0.78–1.65 |
| CA19-9 > 37 U/mL | 63.9 | 1.52 | 0.044 | 1.01–2.27 |
| Alb <4.0 g/dL | 106.2 | 1.12 | 0.70 | 0.64–1.96 |
| PNI[a] < 45.7 | 82.3 | 1.55 | 0.08 | 0.94–2.61 |
| Preoperative Biliary Drainage | 106.2 | 1.14 | 0.55 | 0.75–1.75 |
| Duration of surgery ≥502 min | 109.5 | 0.95 | 0.80 | 0.64–1.40 |
| Amount of blood loss ≥522 mL | 116.1 | 0.93 | 0.74 | 0.61–1.43 |
| Intraoperative transfusion | 88.4 | 1.19 | 0.50 | 0.71–1.92 |
| Adjuvant chemotherapy | 106.2 | 0.81 | 0.36 | 0.50–1.27 |
| Gross appearance; ulcerative and mixed type | 35.6 | 1.38 | 0.11 | 0.93–2.03 |
| Tumor differentiation; except for well-differentiated tumor | 63.9 | 1.65 | 0.016 | 1.10–2.52 |
| Histological subtypes; except for intestinal type | 98.6 | 1.15 | 0.50 | 0.78–7.71 |
| Maximum diameter of the tumor ≥12 mm | 119.1 | 1.50 | 0.17 | 0.85–2.83 |
| T-stage; pT2 or more | 97.0 | 1.66 | 0.053 | 0.99–2.84 |
| Portal vein invasion | 24.5 | 2.69 | 0.19 | 0.56–9.20 |
| INF b/c | 116.1 | 0.38 | 0.002 | 0.21–0.69 |
| Ly+ | 55.3 | 1.09 | 0.70 | 0.71–1.67 |
| V+ | 70.2 | 1.62 | 0.027 | 1.06–2.47 |
| Pn+ | 82.2 | 0.83 | 0.43 | 0.52–1.32 |
| N+ | 52.5 | 2.01 | 0.002 | 1.30–3.11 |
| R1 | 27.1 | 1.12 | 0.83 | 0.38–2.73 |

Abbreviations: Alb, serum albumin level; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Ly. microscopic lymphatic invasion; MST, median survival time; N, nodal involvement; Pn, microscopic perineural invasion; PNI, prognostic nutrition index; R1; microscopic residual tumor; V, microscopic venous invasion.

[a]PNI was calculated as 10 × albumin (g/dl) + 0.005 × total lymphocyte count (no./mm$^3$).

or more in 72 and 6 months or more in 53 patients. Eventually, 40 patients who received AC had recurrence. Among them, 11 patients relapsed during AC, and seven patients had tumor recurrence within 6 months after curative surgery.

As a result of PSM, 63 patients each were assigned to both groups. Patient characteristics were almost similar between patients with and without AC (Table 6). RFS was comparable between the two groups (hazard ratio; 0.85, $p = 0.54$, 95% CI; 0.51–1.42; Figure 3).

### 3.8 | Identification of the potential candidates for NAC

The potential candidates for NAC would be the patients whose maximum diameter of the tumor ≥12 mm, who have pT≥2 tumor, PV+, V+, and/or N+. Table 7 showed positive/negative predictive value and risk ratio of preoperatively detectable parameters which independently predicted maximum diameter of the tumor ≥12 mm, pT≥2 tumor, V+, and N+ prior to surgery obtained from multivariate analysis with a logistic regression model. PV+ was excluded from the analysis since it would be possible to be diagnosed by preoperative imaging.

The alternative approach to identify the potential candidate for NAC was performed by multivariate analysis by Cox proportional hazard model on RFS using only preoperative parameters. As a result, CA19-9 > 37 U/mL (Hazard ratio [HR]; 1.80, $p = 0.015$, 95% CI; 1.25–2.58), gross appearance of ulcerative and mixed type (HR; 1.77 $p = 0.002$, 95% CI; 1.24–2.50), and tumor differentiation except for well-differentiated tumor (HR; 1.62, $p = 0.008$, 95% CI; 1.13–2.32).

Thus, patients with (1) CA19-9 > 37 U/mL ($n = 149$), (2) requiring preoperative biliary drainage ($n = 263$), (3) whose gross appearance of the tumor is ulcerative or mixed type ($n = 114$), and (4) whose tumor differentiation is except for well-differentiated tumor ($n = 195$) in the present cohort would be the candidate for NAC.

## 4 | DISCUSSION

The present study showed that aged ≥71, maximum diameter of the tumor ≥12 mm, pT≥2, V+, and pN+ were independent prognostic

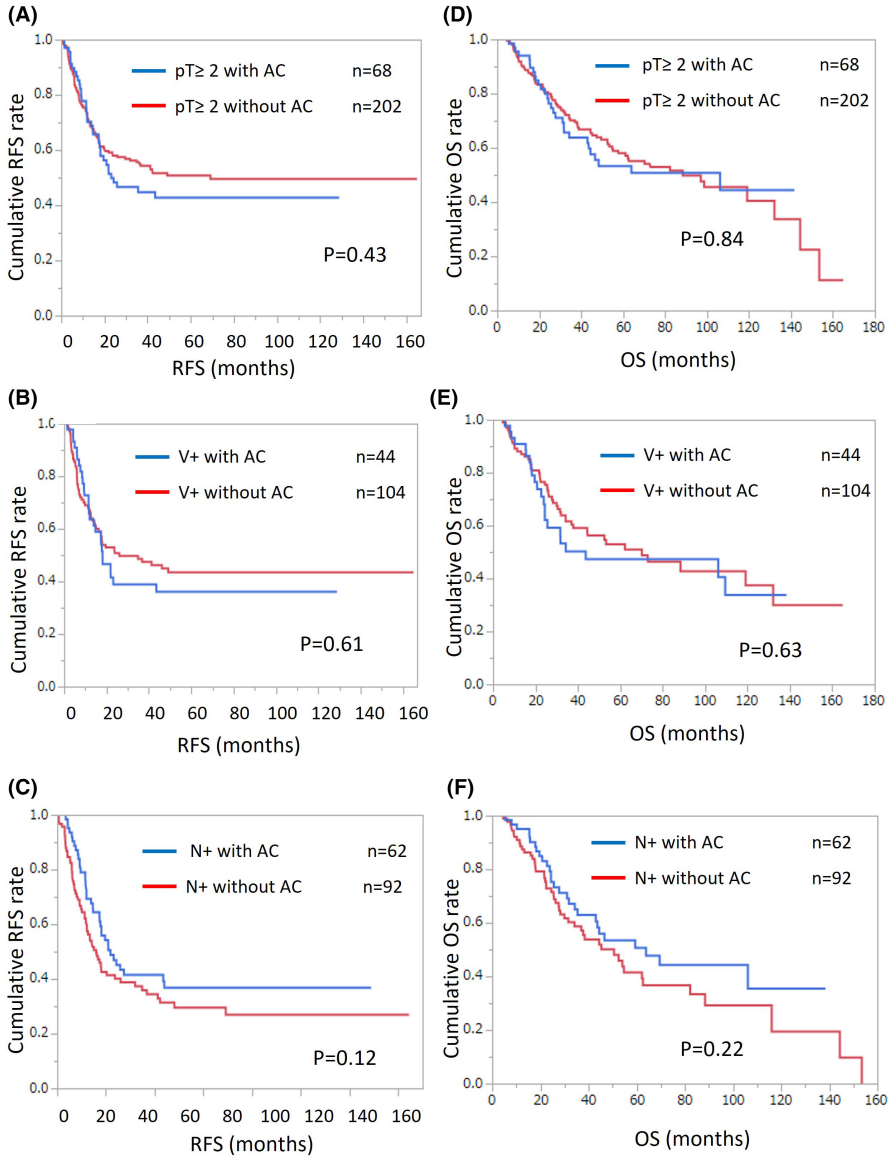


**FIGURE 2** Kaplan–Meier curves of RFS and OS in patients with poor prognostic factors RFS curves for patients with pT≥2 (A), V+ (B), and pN+ (C). OS curves for patients with pT≥2 (D), V+ (E), and pN+ (F).

factors for poor RFS in the cohort of 460 patients with CAV. A PSM showed that AC was not effective in this population. Clinical variables including CA19-9 > 37 U/mL, tumor differentiation except for well-differentiated tumor, and histological subtypes except for intestinal type independently predicted pT≥2, V+, and pN+. To improve the prognosis of CAV patients with at high-risk for recurrence, NAC may be an option.

The prognostic factors associated with shorter RFS in the present study were almost similar with those of the previous series.[1–5] The point of difference was that histological subtype was not an independent factor associated with poor prognosis in the present study. Given its anatomical specificity, three different histological subtypes have been identified in CAV, including intestinal, pancreatobiliary, and mixed type. Since first reported by Kimura et al. in 1994,[16] histological subtype of CAV has been discussed as one of the prognostic factors.[4] Recently, two large retrospective multicenter cohort studies evaluated the impact of histological subtypes on prognosis in patients with CAV.[7,17] Both studies concluded that pancreatobiliary and mixed type was one of the prognostic factors associated with shorter RFS. However, 34% and 38% of study subjects in each study had missing data regarding histological subtype, which could potentially affect the reliability of results. In the present study, pancreatobiliary and mixed type was one of the prognostic factors associated with shorter RFS but not an independent prognostic factor through multivariate analysis, and only three patients had missing data regarding histological subtypes of CAV. Another point of difference was that AC was an unfavorable prognostic factor in the present study. With regard to AC for patients with CAV, two large retrospective multicenter observational studies reported that it had a positive impact on patient prognosis,[6,7] meanwhile another large retrospective study reported no beneficial impact of adjuvant therapy on patient prognosis.[9] This was based on the facts that an AC regimen varied a great deal since there were not established protocols for optimal management after curative resection of CAV, and no previous studies showed detailed information about chemotherapy dose and duration. And very often, it was the case that patients

**TABLE 6** A comparison of clinicopathological variables between patients with and without adjuvant chemotherapy before and after propensity score matching (PSM).

| | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Ad. Chemo + | Ad. Chemo − | | Ad. Chemo + | Ad. Chemo − | |
| | *N* = 80 | *N* = 380 | *p* value | *N* = 63 | *N* = 63 | *p* Value |
| Male/Female | 48 (60%) | 226 (59%) | 1.00 | 36/27 | 39/24 | 0.71 |
| Age ≥ 71 | 38 (48%) | 212 (56%) | 0.22 | 31 (49%) | 31 (49%) | 1.00 |
| Preoperative BMI (kg/m$^2$) | 22.2 ± 0.4 | 22.1 ± 0.2 | 0.76 | 22.1 ± 0.4 | 22.3 ± 0.4 | 0.88 |
| Preoperative biliary drainage | 58 (73%) | 208 (55%) | 0.004 | 47 (75%) | 47 (75%) | 1.00 |
| Alb (g/dL) | 3.8 ± 0.1 | 3.8 ± 0.1 | 0.93 | 3.7 ± 0.1 | 3.7 ± 0.1 | 0.54 |
| PNI | 46.3 ± 0.8 | 45.9 ± 0.4 | 0.65 | 45.6 ± 0.9 | 45.0 ± 0.9 | 0.65 |
| CEA (ng/mL) | 3.4 ± 0.4 | 3.2 ± 0.2 | 0.68 | 3.0 ± 0.3 | 3.2 ± 0.3 | 0.59 |
| CA19-9 (U/mL) | 588 ± 483 | 510 ± 221 | 0.88 | 181 ± 198 | 551 ± 193 | 0.18 |
| Duration of surgery (min) | 479 ± 13 | 461 ± 6 | 0.20 | 471 ± 15 | 453 ± 15 | 0.42 |
| Amount of blood loss (ml) | 789 ± 62 | 761 ± 28 | 0.68 | 812 ± 74 | 796 ± 73 | 0.88 |
| Intraoperative transfusion | 12 (15%) | 57 (15%) | 1.00 | 12 (19%) | 13 (21%) | 1.00 |
| CR-POPF | 22 (28%) | 142 (37%) | 0.10 | 19 (30%) | 25 (40%) | 0.35 |
| Major complication[a] | 18 (23%) | 98 (26%) | 0.57 | 15 (24%) | 18 (29%) | 0.69 |
| Gross appearance; ulcerative and mixed type | 29 (36%) | 85 (22%) | 0.015 | 22 (35%) | 21 (33%) | 1.00 |
| Maximum diameter of the tumor ≥12 mm | 70 (88%) | 300 (79%) | 0.09 | 56 (89%) | 53 (84%) | 0.60 |
| Tumor differentiation; except for wel | 54 (68%) | 141 (37%) | <0.01 | 43 (68%) | 40 (63%) | 0.71 |
| Histological subtypes; except for intestinal type | 61 (77%) | 181 (48%) | <0.01 | 48 (76%) | 45 (71%) | 0.69 |
| T-stage; pT2 or more | 66 (83%) | 204 (54%) | <0.01 | 53 (84%) | 52 (83%) | 1.00 |
| Portal vein invasion | 0 | 3 (0.8%) | 1.00 | 0 | 2 (3.2%) | 0.50 |
| INF b/c | 75 (96%) | 255 (77%) | <0.01 | 61 (97%) | 62 (98%) | 1.00 |
| Ly+ | 50 (63%) | 115 (30%) | <0.01 | 38 (60%) | 42 (67%) | 0.58 |
| V+ | 42 (53%) | 106 (28%) | <0.01 | 32 (51%) | 33 (52%) | 1.00 |
| Pn+ | 40 (51%) | 56 (15%) | <0.01 | 28 (44%) | 24 (43%) | 0.59 |
| N+ | 61 (77%) | 93 (24%) | <0.01 | 44 (70%) | 43 (68%) | 1.00 |
| R1 | 4 (5%) | 6 (2%) | 0.08 | 3 (5%) | 5 (8%) | 0.72 |

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; Alb, serum albumin level; PNI, prognostic nutrition index; Ly. microscopic lymphatic invasion; V, microscopic venous invasion; Pn, microscopic perineural invasion; N, nodal involvement, R1; microscopic residual tumor.

[a]PNI was calculated as 10 × albumin (g/dL) + 0.005 × total lymphocyte count (no./mm$^3$).

who received AC more likely had poor prognostic factors than patients without AC. That is inherent in their retrospective nature, limited to conclude the impact of AC on patients' prognosis. It is also the case in the present study. Only a prospective trial with a rigorous protocol can guarantee highly reliable data. Recently. there have been four randomized control trials evaluating the efficacy of AC in patients with biliary tract cancer who underwent curative resection. Only one study (JCOG1202, ASCOT[18]) included patients with CAV, but the others (BILCAP,[19] PRODIGE 12-ACCORD 18,[20] BCAT[21]) did not. The ASCOT demonstrated that AC with S-1 had a significant benefit in improving overall survival, and it would become a standard of care for biliary tract cancer patients after curative surgery. On the other hand, adjuvant chemotherapy has a drawback inherent to chemotherapy after highly invasive surgery, such as PD. Indeed, one-quarter of patients could not achieve adjuvant chemotherapy due to their condition or disease progression in the ASCOT study.[18] Although overall survival was significantly improved in patients with AC, about half of the patients had recurrence regardless of AC in study population of the ASCOT, as well as the present study, and about one-third of the patients with recurrence of the present study relapsed within 6 months after surgery. Thus, only AC may not be enough, and an additional therapeutic option would be necessary to prevent recurrence and to achieve further improvement of survival in a specific population of CAV.

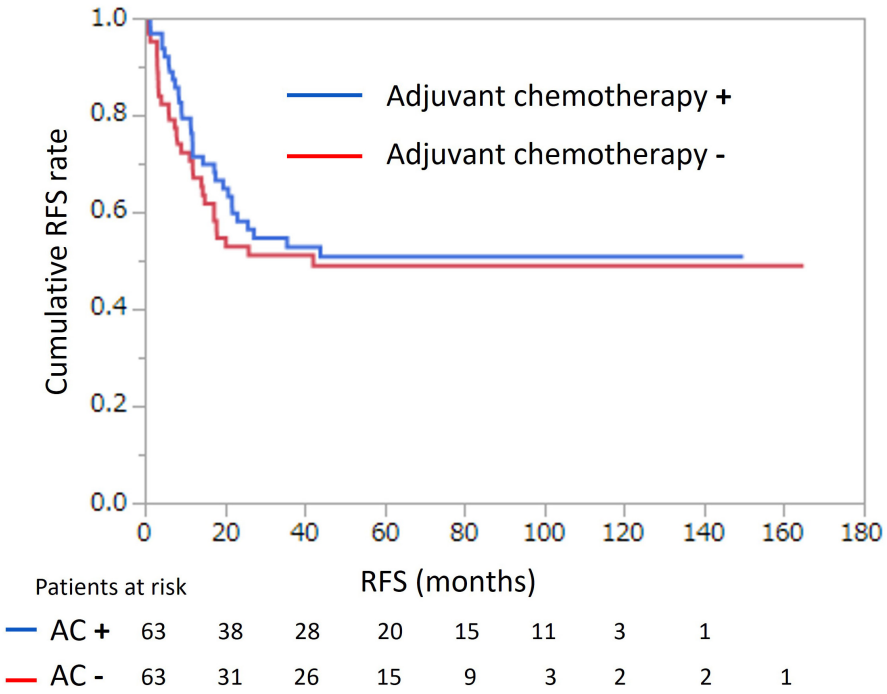


FIGURE 3 Kaplan–Meier RFS curve.

New strategies including NAC have been investigated in the treatment landscape of resectable pancreatic cancer. The rationale of NAC is considered to guarantee early delivery of systemic chemotherapy, leading to increase in the chance of a resection without microscopic residual tumor (R0)[22] and suppression of micrometastasis.[23] Furthermore, all patients who planned to have surgery may be able to benefit from preoperative chemotherapy. Although two recent prospective trials failed to prove overall survival benefit of neoadjuvant chemo- or chemoradiotherapy for patients with resectable pancreatic cancer,[24,25] the Prep-02/JSAP-05 trial demonstrated the survival benefit of NAC for resectable pancreatic cancer.[26] In this context, NAC becomes a standard of care for resectable pancreatic cancer in Japan. Based on these backgrounds, NAC for not all but a specific population of CAV patients may be useful. In the present study, as expected, maximum diameter of the tumor ≥12 mm, pT ≥2, PV+, V+, and N+ were independent prognostic factors for poor RFS. Nodal involvement, precise tumor size, and tumor depth cannot always be diagnosed accurately prior to surgery and microvascular invasion even more so. The result of the present study showed that CA19-9 > 37 U/mL, gross appearance of ulcerative and mixed type, tumor differentiation except for well-differentiated tumor, and preoperative biliary drainage were significantly associated with pT ≥2, V+, N+, and maximum diameter of the tumor ≥12 mm. In the future, the clinical trial aiming to explore the efficacy of NAC for CAV patient who have at least one of the above preoperative factors or who are diagnosed with PV+ by preoperative imaging may be desirable.

The present study had several limitations. First, although the present study consisted of a large cohort of patients with CAV despite its rarity, this was a retrospective study. Several data, particularly histological subtype and perineural invasion in three patients, and CA19-9 in four patients, were missing. This might bias the study results, while the proportion of missing data was relatively small (less than 1% of study population), and we considered that it might not matter as much. Therefore, we did not use the imputation of missing values, but used a list-wise deletion for missing data. Second, the assessment of histological subtype was performed by local pathologists in each center and not validated by multiple pathologists, suggesting that there would be a certain level of disagreement between the pathologists. A classification of histological subtype was implemented using hematoxylin and eosin staining according to the WHO Classification of Tumors of the Digestive system (5th edition),[15] while immunohistochemical analysis using cytokeratin and apomucin might be able to minimize the disagreement between each pathologist.[27] Third, we did not evaluate other tumor biology biomarkers such as KRAS, APC, TP53, and ELF3.[28] Identification of the targeted genes would be able to perform personalized therapy, and may be able to determine the candidate for NAC. Forth, although a PSM was performed to minimize the bias for evaluation of the efficacy or AC in this population, chemotherapy regimen was too heterogeneous, and the analysis was implemented regardless of dose intensity or duration. Therefore, we were unable to get conclusive results in terms of the role of AC on CAV. Fifth, the primary outcome was set as RFS in the present study, which was defined as the duration from the time of curative surgery for CAV until the time recurrence is first documented by imaging modalities. Of course, RFS is a recommended endpoint according to both the European Medicines Agency and United States Food and Drug Administration since it can be a surrogate for overall survival and patients' quality of life.[29,30] An important issue that may be a limitation of this endpoint lies in what is labeled "recurrent disease." The interval is sensitive to how disease is documented and how frequently it is assessed[31] In the present study, the median duration between the date of documented recurrence and the date of the most recently performed imaging before being diagnosed with recurrence was 3.7 months in 143 patients with tumor

**TABLE 7** Predictive factors for pT≥2 tumor, V+, N+, and maximum diameter of the tumor ≥12 mm.

| | Positive predictive value | Negative predictive value | Risk ratio | 95% CI |
|---|---|---|---|---|
| pT ≥2 tumor | | | | |
| CA19-9 > 37 U/mL | 81.8% | 53.2% | 2.91 | 1.70–4.97 |
| PNI[a] < 45.7 | 73.8% | 55.7% | 2.15 | 1.19–3.88 |
| Preoperative biliary drainage | 74.8% | 63.4% | 2.38 | 1.46–3.91 |
| Gross appearance; ulcerative and mixed type | 74.6% | 46.5% | 2.13 | 1.19–3.84 |
| Tumor differentiation; except for well-differentiated tumor | 79.0% | 56.2% | 2.88 | 1.75–4.73 |
| V+ | | | | |
| CA19-9 > 37 U/mL | 46.5% | 75.1% | 1.64 | 1.04–2.58 |
| Preoperative biliary drainage | 41.7% | 80.9% | 1.69 | 1.03–2.76 |
| Gross appearance; ulcerative and mixed type | 51.8% | 74.3% | 1.49 | 1.03–2.76 |
| Tumor differentiation; except for well-differentiated tumor | 50.8% | 81.5% | 2.31 | 1.48–3.61 |
| N+ | | | | |
| CA19-9 > 37 U/mL | 47.2% | 73.4% | 1.74 | 1.09–2.78 |
| Alb <4.0 g/dL | 38.8% | 79.3% | 2.47 | 1.26–4.86 |
| Gross appearance; ulcerative and mixed type | 44.7% | 70.2% | 2.56 | 1.55–4.23 |
| Tumor differentiation; except for well-differentiated tumor | 48.2% | 77.4% | 3.30 | 2.08–5.24 |
| Maximum diameter of the tumor ≥ 12 mm | | | | |
| Preoperative biliary drainage | 86.7% | 27.8% | 2.18 | 1.32–3.58 |
| BMI < 21 kg/m$^2$ | 90.5% | 26.1% | 3.04 | 1.71–5.40 |

Abbreviations: Alb, serum albumin level; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; N, nodal involvement; PNI, prognostic nutrition index; V, microscopic venous invasion.

recurrence, and 21 patients had more than 6 months interval between the date of documented recurrence and the date of the most recently performed imaging before being diagnosed with recurrence.

## 5 | CONCLUSION

In the cohort of 460 patients with CAV, aged ≥71, maximum diameter of the tumor≥12 mm, pT≥2, V+, and pN+ were independent prognostic factors for poor RFS. A PSM in this population did not show a beneficial effect of AC. An additional therapeutic strategy may be desirable in CAV patients at high risk for recurrence.

### AUTHOR CONTRIBUTIONS

Narita M designed this research, acquired the data, and drafted the article. Kitamura K, Fukumitsu K, Kitagawa H, Mori A, Yazawa T, Terajima H, Kitaguchi K, and Hata T acquired the data and revised the article. Hatano E contributed to the analysis and interpretation of data. All authors contributed to the final approval of the manuscript.

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### CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest for this article.

## ETHICS STATEMENTS

Approval of the research protocol: The protocol of this study was approved by the Central Institutional Review Board in Kyoto Medical Center (approval number; 21–071) and was in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Informed Consent: The need for informed consent was waived because of the retrospective design of the study. Patient consent for participation was obtained using the opt-out method in each center.

Registry and the Registration No. of the study: N/A.

Animal Studies: N/A.

## ORCID

*Masato Narita* https://orcid.org/0000-0002-7872-0724

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## APPENDIX

### DISCUSSANT

#### PROFESSOR TOSHIMI KAIDO

First of all, congratulations on your successful performance of multicenter clinical study. I have three questions.

First, in the present study, chemotherapy regimen, including dose intensity and duration, are too heterogeneous. In such a situation, it is very difficult to draw any definite conclusions. Do you investigate the efficacy of adjuvant chemotherapy for patients who could complete adjuvant chemotherapy?

Second, as you know, abdominal body compositions, including skeletal muscle mass or visceral adiposity, have a negative impact on outcomes in HPB surgery. Did you examine the impact of such abdominal body compositions on outcomes in this study?

Finally, in your study, about 60% underwent biliary drainage due to obstructive jaundice or cholangitis. In these situations, albumin level usually decreases due to inflammation caused by ERCP or cholangitis. But in your study, you measured albumin and BMI as nutrition parameters. In such a situation, they are not good nutritional parameters because CRP level increases. How do you think about that?

#### DR. MASATO NARITA RESPONSE

Thank you, Professor Kaido, and thank you for your comments.

That is one of the biggest limitations of the present study. Of 80 patients who received adjuvant chemotherapy, 53 patients received adjuvant chemotherapy for six months or more, so maybe we can say that it's a completion of chemotherapy. When we performed the survival analysis of these patients versus other patients, there was no difference about the RFS.

We had a great interest in the impact of abnormal body compositions including sarcopenia on survival. Before this evaluation, some of us suggested to evaluate the relationship between sarcopenia and overall survival. We tried, but it was too difficult to collect the data without a lot of missing data. But when we perform a prospective study in the future, we will do that.

As for nutritional parameters, we collected nutritional data just before the surgery. I suppose CRP level was not so high before surgery, because patients underwent surgery after improvement of inflammation.

#### PROFESSOR TSUTOMU FUJII

First, why did the authors focus on the analysis on progression-free survival, not overall survival? Did the authors perform the analysis on overall survival?

Second, have the authors considered the extent and the number of lymph node dissection in this analysis? Because that is much different from institution to institution.

#### DR. MASATO NARITA RESPONSE

There were three reasons. First, from the viewpoint of cancer statistics, RFS may be less important than OS. But from the viewpoint of clinical practice, it is sure that once cancer relapsed, patient QOL will dramatically change into worse. We believe that the study aiming at improvement of RFS must be important.

Second, according to the guidance document both, the European Medicine Agency and USFDA, RFS can be a valid surrogate for OS. Indeed, almost all patients died after recurrence in the present study.

Third, we evaluated overall survival, 149 patients died during the study period and among them, 59 patients died of other reasons. It's too large to precisely evaluate the event of cancer recurrence and cancer death, so we used RFS instead of OS. We evaluated the overall survival, but there was not so big difference between the RFS and the overall survival.

We didn't evaluate the lymph node station number, but we analyzed the lymph node ratio. It means that the ratio of number of metastatic lymph node to harvested lymph node, to minimize the bias among the institution. However, patients with LN ratio more than 0 was significantly associated with poor prognosis. It may be because the prognostic power of nodal positive disease was too strong in patients with CAV.

#### PROFESSOR MASAYUKI SHO

You showed us very similar results of RFS with OS. That means the chemotherapy, at least current chemotherapy has no impact on the recurrence. Also, you showed us that adjuvant chemotherapy had no impact on patient prognosis. Based on such data, why can you say that the future strategy is neoadjuvant chemotherapy?

In addition, it may be important to examine the efficacy according to each regimen of chemotherapy.

#### DR. MASATO NARITA RESPONSE

When we look at the ASCOT study, more than one-fourth patients could not receive adjuvant chemotherapy in the treatment group because of the tumor progression or worse patient condition after surgery. That is the weakness of adjuvant chemotherapy. On the other hand, neoadjuvant chemotherapy can be performed on all patients who plan to undergo surgery. With neoadjuvant chemotherapy, we may be able to inhibit tumor progression before surgery. Therefore, neoadjuvant chemotherapy would be desirable. As you told me, we don't have any effective chemotherapy regimen so far in patients with CAV. That's a very important issue that should be addressed.