Preoperative risk factors for early recurrence after resection of perihilar cholangiocarcinoma

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Abstract

Background: Early recurrence after curative resection of perihilar cholangiocarcinoma (PHCC) often occurs within a year of surgery. Preoperative predictors of early recurrence remain unclear. The aim of this study was to define reliable preoperative predictors of early recurrence.

Methods: Medical records and preoperative multidetector-row CT of patients with PHCC who underwent resection between 2002 and 2018 were reviewed. Clinical findings, tumour markers, and radiological appearances including a ‘periductal enation sign’ (PES) where there was evidence of soft tissue enhancement appearing to arise from the extrahepatic bile duct, were analysed.

Results: Among 261 patients who underwent resection for PHCC, 67 (25.7 per cent) developed early recurrence. Multivariable analysis identified four preoperative risk factors for early recurrence, namely carbohydrate antigen 19–9 (CA19-9) 37 U/ml or higher (OR 2.19, 95 per cent confidence interval (c.i.) 1.08 to 4.46), positive PES (OR 7.37, 95 per cent c.i. 2.46 to 22.10), mass-forming tumour (OR 4.52, 95 per cent c.i. 2.11 to 9.68). The OR of preoperative risk factors were used to define four risk subgroups for early recurrence. The early recurrence rates in the low, moderate, high, and very-high risk groups were 0, 9.4, 39.7, and 65.0 per cent respectively.

Conclusion: CA19-9, PES, mass-forming tumour, and luminal-occlusion tumour identify patients at higher risk for early recurrence after resection of PHCC.

Introduction

Surgical resection is the cornerstone to achieve long-term survival in perihilar cholangiocarcinoma (PHCC)1–3. Around 24–30 per cent of patients who have undergone resection develop early recurrence within a year of their operation with a dismal prognosis4–6. A detailed analysis of preoperative factors that might predict early recurrence has yet to be described, although some studies have reported risk factors for early recurrence after the resection using both preoperative and postoperative factors5–7. Recently, the present authors8 reported the periductal enation sign (PES) on preoperative multidetector-row CT (MDCT) as being associated with perineural invasion, poor outcomes, and shortened survival in resected distal cholangiocarcinoma. The possible relationship between PES and tumour radiological appearance for predicting perineural invasion and early recurrence in PHCC has not yet been clarified.

The present study aimed to identify preoperative risk factors associated with early recurrence after resection of PHCC.

Methods

This study was approved by the institutional ethics committee (approval number J2019-142-2019-1-3) and is reported in accordance with the STROBE statement9. The medical records and MDCT scans of patients with PHCC who underwent resection with curative intent at Shizuoka Cancer Center between September 2002 and December 2018 were analysed. In-hospital deaths after surgery were excluded. All patients underwent major hepatectomy and bile duct resection with or without vascular resection or pancreatoduodenectomy10. The Bismuth classification was used to assess the extent of the tumour11. The plasma disappearance rate of indocyanine green clearance (ICGK) and future liver remnant volume were utilized to evaluate the functional reserve of the remnant liver12. The ASA physical status (PS)13 and Charlson co-morbidity index14 were used for preoperative assessments. The preoperative carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) values were usually measured within 2 weeks before the day of surgery, after the resolution of jaundice and cholangitis. Neoadjuvant treatment was never performed. Early recurrence was defined as recurrence within 1 year of resection of PHCC5.

MDCT analysis

A MDCT with a standard protocol optimized for cholangiocarcinoma was used for preoperative tumour assessment before biliary stent placement. MDCT was performed in the early arterial, late arterial, portal venous, and delayed phases. Raw data were reconstructed...
with a slice thickness of 2 mm. MDCT images were reviewed by experienced radiologists blinded to the other clinical findings.

As described previously, PES was defined as a surrounding soft tissue enhancement that seemed to emanate from the circumference of the enhanced extrahepatic bile duct at MDCT (Fig. 1a). The length of PES was defined as the perpendicular distance from the circumference of the bile duct to the vertex of the enation, and a positive PES was defined as a PES length of 2 mm or more (Fig. 1b). A mass-forming PHCC was defined when an extraductal mass was identified (Fig. 1c). Intraductal tumour appearance was divided into ‘luminal occlusion’ where the lumen of the bile duct was completely invisible (Fig. 1d) and ‘non-luminal occlusion’ where the lumen remained visible (Fig. 1e,f). The tumour abutment angle of the portal vein (PV) or hepatic artery (HA) was assessed, with an angle of 180° or more considered significant. Lymphadenopathy was defined as the detection of enhancing round-shaped lymph nodes with a short diameter of 1 cm or more within the regional lymph node area.

**Fig. 1** The tumour radiological appearance on multidetector-row CT

a The arrowhead indicates the PES. b The length of the PES was defined as the perpendicular distance from the circumference of the bile duct to the vertex of the enation (arrow). c The arrowhead indicates the mass-forming tumour. d The arrowhead indicates a luminal-occlusion tumour. e,f The arrowhead indicates a non-luminal-occlusion tumour. PES, periductal enation sign; PV, portal vein; RHD, right hepatic duct; CHD, common hepatic duct; LHD, left hepatic duct.
Postoperative follow-up

Pathological examinations were performed in accordance with the International Union Against Cancer (UICC) TNM Classification eighth edition. Adjuvant treatment was not routinely performed, except for patients who participated in clinical trials (13 patients) and those who had a positive surgical margin at final pathology (18 patients).

Clinical and radiological follow-up was scheduled on a 3-month basis for the first year after resection. Recurrence was diagnosed either through radiological or histological evidence.

Table 1. Site of initial recurrence according to early recurrence

| Location                  | ER (n = 67) | Non-ER (n = 194) | P    |
|---------------------------|-------------|------------------|------|
| Locoregional              | 11 (16)     | 29 (15)          | 0.844|
| Distant metastasis*       | 66 (99)     | 74 (38)          | <0.001|
| Liver                     | 31 (46)     | 25 (13)          | <0.001|
| Peritoneum                | 21 (31)     | 25 (13)          | 0.001|
| Lymph node                | 19 (28)     | 18 (9)           | <0.001|
| Lung                      | 11 (16)     | 18 (9)           | 0.118|
| Others                    | 6 (9)       | 7 (4)            | 0.103|

Values are n (%). *Including overlap. ER, early recurrence.

Table 2. Clinicopathologic characteristics according to early recurrence

| Characteristic                        | ER (n = 67) | Non-ER (n = 194) | P    |
|--------------------------------------|-------------|------------------|------|
| Preoperative characteristics          |             |                  |      |
| Age (years), median (i.q.r.)          | 70 (64–75)  | 70 (65–75)       | 0.872|
| Sex ratio (M:F)                       | 48:19       | 132:62           | 0.647|
| BMI (kg/m²), median (i.q.r.)          | 21.7 (19.6–23.6) | 21.8 (20.0–23.7) | 0.613|
| ASA-PS grade ≥III                    | 11 (16)     | 20 (10)          | 0.193|
| Charlson co-morbidity index, median (i.q.r.) | 4 (3–5)     | 4 (3–5)          | 0.905|
| Albumin (g/dl), median (i.q.r.)       | 3.9 (3.6–4.1) | 4.0 (3.6–4.3)    | 0.124|
| ICGK, median (i.q.r.)                 | 0.144 (0.137–0.171) | 0.152 (0.136–0.175) | 0.598|
| Remnant liver volume (%), median (i.q.r.) | 46 (34–70)  | 47 (39–62)       | 0.605|
| CA19-9 (U/ml), median (i.q.r.)        | 148 (41–792)| 47 (18–166)      | <0.001|
| CEA (ng/ml), median (i.q.r.)          | 3.5 (1.7–5.1) | 2.5 (1.5–3.7)    | 0.025|
| Biliary drainage                     | 46 (69)     | 131 (68)         | >0.999|
| Cholangitis                          | 17 (25)     | 40 (21)          | 0.493|
| PV embolization                      | 36 (54)     | 96 (50)          | 0.573|
| Bismuth type, IV                     | 19 (28)     | 63 (33)          | 0.647|
| MDCT findings                        |             |                  |      |
| PES-positive                         | 61 (91)     | 135 (70)         | <0.001|
| Mass-forming                         | 21 (31)     | 28 (14)          | 0.004|
| Luminal occlusion                    | 57 (85)     | 93 (48)          | <0.001|
| Abutment to PV                       | 32 (48)     | 81 (42)          | 0.395|
| Abutment to HA                       | 38 (57)     | 107 (53)         | 0.887|
| Lymphadenopathy                      | 24 (36)     | 72 (37)          | 0.884|
| Surgical outcomes                    |             |                  |      |
| Hepatocarcinoma type, right-side      | 34 (51)     | 83 (43)          | 0.319|
| Combined vascular resection          | 25 (37)     | 68 (35)          | 0.768|
| Combined pancreaticoduodenectomy     | <0.001      | 40 (21)          | 0.370|
| Operating time (min), median (i.q.r.) | 578 (477–653)| 553 (477–645)   | 0.587|
| Blood loss (g), median (i.q.r.)       | 1447 (966–1986)| 1339 (944–1886) | 0.326|
| Blood transfusion                    | 18 (27)     | 65 (34)          | 0.363|
| Postoperative outcomes               |             |                  |      |
| Complication, grade ≥3*              | 27 (40)     | 87 (45)          | 0.569|
| pT3–4†                               | 43 (64)     | 93 (48)          | 0.024|
| pN1–2†                               | 43 (64)     | 66 (34)          | <0.001|
| pM1†                                 | 10 (15)     | 6 (3)            | 0.001|
| Histology, G2–3                       | 51 (76)     | 111 (57)         | 0.006|
| Perineural invasion                  | 56 (84)     | 144 (74)         | 0.134|
| Surgical margin positive             | 12 (18)     | 27 (14)          | 0.431|
| Adjuvant treatment                   | 6 (9)       | 25 (13)          | 0.513|

Values are n (%), †According to the UICC 8th edition. ER, early recurrence; ASA-PS, ASA physical status; ICGK, plasma disappearance rate of indocyanine green clearance; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; MDCT, multidetector-row computed tomography; PES, periductal enation sign; PV, portal vein; HA, hepatic artery.

Statistical analyses

Continuous data were described as medians with interquartile ranges and compared using the Mann–Whitney U test. Categorical variables were compared using Fisher’s exact test. A logistic regression analysis using stepwise backward selection was performed with multivariable analysis to determine preoperative risk factors for early recurrence after the resection of PHCC. All preoperative variables were entered into the model, and those with a P ≥ 0.050 were removed from the final model by backward selection. Factors found to be significant according to multivariable analysis were given weighting points based on their ORs. The factor with the lowest OR was given one point and depending on the ratio of the OR in the other factors to it, two or three points were given. Those points were then summed and divided into four risk subgroups (low, 0–2 points; moderate, 3–4 points; high, 5–6 points; and very-high, 7–8 points). Survival curves were generated using the Kaplan–Meier methods, and differences were compared using the log rank test. Two-sided P values <0.050 were considered statistically significant. The statistical analyses were performed using R (version 4.1.0, The R Foundation for Statistical Computing, Vienna, Austria).
Table 3. Preoperative risk factors associated with early recurrence

| Risk Factor                          | n   | ER (%) | OR (95% c.i.) | P    | Multivariable  |
|--------------------------------------|-----|--------|---------------|------|----------------|
|                                      |     |        |               |      | OR*            |
| Age (years)                          |     |        |               |      |                |
| <75                                  | 193 | 25.4   | 1.00 (reference) | 0.861 | –              |
| ≥75                                  | 68  | 26.5   | 1.06 (0.56–1.98) | –     | –              |
| Sex ratio (M:F)                      |     |        |               |      |                |
| Female                               | 81  | 23.5   | 1.00 (reference) | 0.583 | –              |
| Male                                 | 180 | 26.7   | 1.19 (0.64–2.19) | –     | –              |
| BMI (kg/m²)                          |     |        |               |      |                |
| <25                                  | 227 | 25.6   | 1.00 (reference) | 0.909 | –              |
| ≥25                                  | 34  | 26.5   | 1.05 (0.46–2.38) | –     | –              |
| ASA-PS score                         |     |        |               |      |                |
| I–II                                 | 230 | 24.6   | 1.00 (reference) | 0.186 | –              |
| III                                  | 31  | 35.5   | 1.71 (0.77–3.78) | –     | –              |
| Charlson co-morbidity index          |     |        |               |      |                |
| <7                                   | 248 | 25.0   | 1.00 (reference) | 0.996 | –              |
| ≥7                                   | 13  | 38.5   | 1.87 (0.59–5.94) | –     | –              |
| Albumin (g/dl)                       |     |        |               |      |                |
| <4.0                                 | 124 | 29.0   | 1.40 (0.90–2.14) | 0.238 | –              |
| ≥4.0                                 | 137 | 22.6   | 1.00 (reference) | –     | –              |
| ICGK                                 |     |        |               |      |                |
| <0.150                               | 125 | 30.4   | 1.61 (0.92–2.82) | 0.095 | –              |
| ≥0.150                               | 136 | 21.3   | 1.00 (reference) | –     | –              |
| Remnant liver volume (%)             |     |        |               |      |                |
| <40                                  | 75  | 26.7   | 1.08 (0.59–1.98) | 0.815 | –              |
| ≥40                                  | 186 | 25.3   | 1.00 (reference) | –     | –              |
| CA19–9 (U/ml)                        |     |        |               |      |                |
| <37                                  | 101 | 13.9   | 1.00 (reference) | <0.001 | 1.00 (reference) |
| ≥37                                  | 160 | 33.1   | 3.08 (1.60–5.92) | –     | 2.19 (1.08–4.46) |
| CEA (ng/ml)                          |     |        |               |      |                |
| <5.0                                 | 201 | 23.3   | 1.00 (reference) | 0.082 | –              |
| ≥5.0                                 | 51  | 35.3   | 1.79 (0.93–3.46) | –     | –              |
| Biliary drainage                     |     |        |               |      |                |
| Absent                               | 84  | 25.0   | 1.00 (reference) | 0.864 | –              |
| Present                              | 177 | 26.0   | 1.05 (0.58–1.91) | –     | –              |
| Cholangitis                          |     |        |               |      |                |
| Absent                               | 204 | 24.5   | 1.00 (reference) | 0.418 | –              |
| Present                              | 57  | 39.8   | 1.31 (0.68–2.51) | –     | –              |
| PV embolization                      |     |        |               |      |                |
| Absent                               | 129 | 24.0   | 1.00 (reference) | 0.549 | –              |
| Present                              | 132 | 27.3   | 1.19 (0.68–2.07) | –     | –              |
| Bismuth type                         |     |        |               |      |                |
| I–II                                 | 179 | 26.8   | 1.00 (reference) | 0.583 | –              |
| IV                                   | 82  | 23.2   | 1.19 (0.64–2.19) | –     | –              |
| PES                                   |     |        |               | <0.001 | –              |
| Negative                             | 61  | 9.2    | 1.00 (reference) | 0.001 | 1.60 (1.82–10.80) |
| Positive                             | 196 | 31.1   | 4.40 (1.60–10.80) | 7.37  | 2.46 (2.46–22.10) |
| Mass formation                       |     |        |               | 0.003 | –              |
| Absent                               | 212 | 21.7   | 1.00 (reference) | 4.46  | –              |
| Present                              | 49  | 42.9   | 2.71 (1.41–5.20) | 0.001 | 4.46 (1.83–10.90) |
| Luminal occlusion                    |     |        |               | <0.001 | –              |
| Absent                               | 11  | 9.0    | 1.00 (reference) | <0.001 | 1.00 (reference) |
| Present                              | 150 | 38.0   | 6.19 (2.99–12.50) | –     | –              |
| Abutment to PV                       |     |        |               | 0.393 | –              |
| Absent                               | 148 | 23.6   | 1.00 (reference) | 4.52  | –              |
| Present                              | 113 | 28.3   | 1.28 (0.73–2.23) | 0.01  | 4.52 (2.11–9.48) |
| Abutment to HA                       |     |        |               | 0.824 | –              |
| Absent                               | 116 | 25.0   | 1.00 (reference) | 0.824 | –              |
| Present                              | 145 | 26.2   | 1.07 (0.61–1.87) | –     | –              |
| Lymphadenopathy                      |     |        |               | 0.850 | –              |
| Absent                               | 165 | 26.1   | 1.00 (reference) | 0.850 | –              |
| Present                              | 96  | 25.0   | 0.95 (0.53–1.69) | –     | –              |

ER, early recurrence; ASA-PS, ASA physical status; ICGK, plasma disappearance rate of indocyanine green clearance; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; PES, periductal enation sign; PV, portal vein; HA, hepatic artery.

**Results**

A total of 261 patients underwent curative resection for PHCC and were analysed. Among these, 67 (25.7 per cent) developed recurrence within 1 year of resection. (Table 1). Regarding recurrence sites, the liver was the most frequent (46.2 per cent), followed by the peritoneum (31.3 per cent), and lymph nodes (28.4 per cent).

Table 2 shows the clinical and pathological characteristics related to early recurrence. Patients who developed early recurrence had higher CA19–9 and CEA values. According to the MDCT findings, a positive PES, mass-forming tumour, and
Fig. 2 The rate of early recurrence according to the risk classification.
\*P = 0.049, \**P < 0.001, \***P = 0.054 (Fisher’s exact test). ER, early recurrence.

Table 4. Pathological features according to carbohydrate antigen 19-9 and multidetector-row CT findings

According to CA19-9

|                     | CA19-9 ≥ 37 U/ml (n = 160) | CA19-9 < 37 U/ml (n = 101) | P   |
|---------------------|-----------------------------|-----------------------------|-----|
| pT3–4*              | 92 (58)                     | 44 (44)                     | 0.031 |
| pN1–2*              | 80 (50)                     | 29 (29)                     | <0.001 |
| pM1*                | 13 (8)                      | 3 (3)                       | 0.114 |
| Histology, G2–3     | 102 (64)                    | 60 (60)                     | 0.514 |
| Perineural invasion | 126 (79)                    | 74 (73)                     | 0.368 |

According to PES

|                     | PES (+) (n = 196) | PES (-) (n = 65) | P   |
|---------------------|------------------|-----------------|-----|
| pT3–4*              | 114 (58)         | 22 (34)         | <0.001 |
| pN1–2*              | 94 (48)          | 15 (23)         | <0.001 |
| pM1*                | 10 (5)           | 6 (9)           | 0.239 |
| Histology, G2–3     | 124 (63)         | 38 (59)         | 0.556 |
| Perineural invasion | 186 (95)         | 14 (22)         | <0.001 |

According to mass formation

|                     | Mass-forming (+) (n = 49) | Mass-forming (-) (n = 212) | P   |
|---------------------|--------------------------|-----------------------------|-----|
| pT3–4*              | 26 (52)                  | 110 (52)                    | >0.999 |
| pN1–2*              | 22 (45)                  | 87 (41)                     | 0.633 |
| pM1*                | 7 (14)                   | 9 (4)                       | 0.016 |
| Histology, G2–3     | 43 (88)                  | 119 (56)                    | <0.001 |
| Perineural invasion | 23 (47)                  | 177 (84)                    | <0.001 |

According to luminal occlusion

|                     | Luminal occlusion (+) (n = 150) | Luminal occlusion (-) (n = 111) | P   |
|---------------------|---------------------------------|---------------------------------|-----|
| pT3–4*              | 88 (59)                         | 48 (43)                         | 0.017 |
| pN1–2*              | 74 (49)                         | 35 (32)                         | 0.005 |
| pM1*                | 8 (5)                           | 8 (7)                           | 0.606 |
| Histology, G2–3     | 113 (75)                        | 49 (44)                         | <0.001 |
| Perineural invasion | 126 (84)                        | 74 (67)                         | 0.002 |

Values are n (%). *According to the UICC 8th edition. CA19-9, carbohydrate antigen 19-9; PES, periductal enation sign.
luminal-occlusion tumour were observed more frequently in the early recurrence group, but the rates of tumour abutment to the PV or HA and lymphadenopathy did not significantly differ.

Multivariable analysis identified four preoperative risk factors that independently predicted early recurrence: CA19-9 of 37 U/ml or higher (OR 2.19), positive PES (OR 7.37), mass-forming tumour (OR 4.46), and luminal-occlusion tumour (OR 4.52) (Table 3). Figure 2 displays the early recurrence rates ranging from 0 to 65 per cent according to the four risk subgroups created from the multivariable analysis, followed by the association with survival (Fig S1).

Correlation between each risk factor and the pathological features is shown in Table 4.

Discussion

Radical surgery represents the cornerstone of PHCC treatment, despite being very invasive, especially once hepatopancreaticoduodenectomy and vascular resection are performed1–3,18–25. The present study has highlighted the importance of early recurrence after resection for PHCC. Predicting the likelihood of early recurrence before surgery could have a profound effect on decision-making for many patients. The present study identified four preoperative risk factors for early recurrence: CA19-9 of 37 U/ml or higher, positive PES, mass-forming tumour, and luminal-occlusion tumour. CA19-9 is a well established prognostic factor in PHCC26,27. The present study revealed that the PES was associated with perineural invasion in PHCC, as shown previously in distal cholangiocarcinoma8; however, while a positive PES was an independent risk factor for early recurrence, perineural invasion was not. Luminal-occlusion tumours were associated with the nature of the highly malignant tumour, which might account for the high early recurrence rate.

A mass-forming tumour was also found as an independent risk factor for early recurrence in the present analysis. Large cohort studies of intrahepatic cholangiocarcinoma showed that 22 per cent of patients developed recurrence within 6 months after surgery26,27, and 44 per cent developed recurrence within 1 year29. PHCC comprehensively includes intrahepatic cholangiocarcinoma with invasion to the hepatic hilum, as it is difficult to clearly distinguish hilar cholangiocarcinoma and intrahepatic cholangiocarcinoma with invasion to the hepatic hilum on clinical images25,30,31. The inclusion of intrahepatic cholangiocarcinoma with mass-forming PHCC may have been responsible for the high early recurrence rate.

To provide a clinically relevant message, a risk classification associated with early recurrence was developed, with increasing rates of recurrence. This identified a group at the highest risk for early recurrence (around 65 per cent) who should be carefully informed about their dismal prognosis before surgery.

The present study has several limitations, including its single-centre and retrospective nature. To validate these results, and in particular, the relatively new concept of PES and luminal occlusion, a multi-institutional study with a large patient population is warranted.

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Disclosure

The authors declare no conflict of interest.

Supplementary materials

Supplementary material is available at BJS Open online.

Data availability statement

The data sets generated and/or analysed during this study are available from the corresponding author on reasonable request.

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