https://doi.org/10.1016/j.hpb.2021.04.011 HPB

ORIGINAL ARTICLE

Outcome after resection for perihilar cholangiocarcinoma in patients with primary sclerosing cholangitis: an international multicentre study

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Abstract

Background: Resection for perihilar cholangiocarcinoma (pCCA) in primary sclerosing cholangitis (PSC) has been reported to lead to worse outcomes than resection for non-PSC pCCA. The aim of this study was to compare prognostic factors and outcomes after resection in patients with PSC-associated pCCA and non-PSC pCCA.

Methods: The international retrospective cohort comprised patients resected for pCCA from 21 centres (2000–2020). Patients operated with hepatobiliary resection, with pCCA verified by histology and with data on PSC status, were included. The primary outcome was overall survival. Secondary outcomes were disease-free survival and postoperative complications.

Results: Of 1128 pCCA patients, 34 (3.0%) had underlying PSC. Median overall survival after resection was 33 months for PSC patients and 29 months for non-PSC patients (p = .630). Complications (Clavien-Dindo grade $\geq$ 3) were more frequent in PSC pCCA (71% versus 44%, p = .003). The rate of post-hepatectomy liver failure (21% versus 17%, p = .530) and 90-day mortality (12% versus 13%, p = 1.000) was similar for PSC and non-PSC patients.

Conclusion: Median overall survival after resection for pCCA was similar in patients with underlying PSC and non-PSC patients. Complications were more frequent after resection for PSC-associated pCCA, with no difference in postoperative mortality.

Received 16 December 2020; accepted 3 April 2021

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This work was presented as an oral abstract at the 14th World Congress of the IHPBA, Virtual Congress, 27–29 November 2020.

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Introduction

Primary sclerosing cholangitis (PSC) is a strong risk factor for cholangiocarcinoma, with PSC patients having a life-time cholangiocarcinoma risk of up to 20%.[1–3] Curative intent resection is the only treatment option for many PSC patients with resectable perihilar cholangiocarcinoma (pCCA) given that liver transplantation for pCCA can only be offered in highly selected cases according to the Mayo protocol (tumour radial diameter < 3 cm, no evidence of lymph node metastasis).[4–6] Moreover, protocols for transplantation in cholangiocarcinoma are not uniformly implemented, and organ availability within transplant programs remains limited. Because the underlying chronic liver disease associated with PSC can increase the risk for postoperative liver failure, a careful evaluation of patients is warranted for resection surgery.[7]

The incidence of pCCA in Western countries is 1–2 per 100 000 individuals per year, and most patients are diagnosed with unresectable tumours.[8,9] In a recent meta-analysis, prognostic factors for shorter overall survival after resection for pCCA were age, lymph node metastasis, microvascular and perineural invasion, tumour-positive resection margin, vascular resection, tumour stage (T3-T4) and tumour differentiation (grade 2–3, i.e. moderate to poor differentiation).[10] In a review of cohorts from both Western and Eastern centres that included over 4000 resected pCCA patients the median overall survival was 34 months.[9]

Resection for cholangiocarcinoma with curative intent in patients with underlying PSC has been claimed to lead to poor survival outcomes, with reviews describing a 3-year overall survival below 20% even for R0 resections.[11,12] However, data on prognosis after resection for perihilar cholangiocarcinoma in PSC are sparse,[13] with current knowledge based on older single-centre case series and mixed cholangiocarcinoma cohorts.[7,11,12,14,15] For instance, in a recent multicentre pCCA cohort study from the United States comparing resection and liver transplantation, only 3 of 191 resected patients had underlying PSC, precluding any conclusions regarding outcomes in PSC pCCA.[4] On the one hand, underlying hepatobiliary disease and immunological aspects of PSC may imply a higher risk of postoperative complications and even tumour recurrence in these patients.[14] On the other hand, modern surveillance in PSC patients may allow the diagnosis of cholangiocarcinoma in earlier stages, improving postoperative outcomes as well as the number of patients eligible for liver transplantation.[16] Evaluation of PSC-specific outcomes after resection of pCCA is therefore warranted.

The aim of this study was to compare prognostic clinicopathological factors and outcomes after resection for pCCA in patients with underlying PSC (PSC pCCA patients) and patients without PSC (non-PSC pCCA patients) in a large international multicentre cohort.

Methods

Study design

Data from a retrospective multicentre cohort compiling outcomes for patients resected for pCCA from 21 European and American centres, members of the Perihilar Cholangiocarcinoma Collaboration Group, were analysed. Variables collected in the cohort included data on preoperative diagnostic and staging modalities, preoperative interventions (such as portal vein embolisation), type of surgery performed, postoperative complications, postoperative pathological diagnosis and staging, tumour recurrence and overall survival. Data on time of PSC diagnosis, preoperative liver function or fibrosis grade were not available in the database. Participating centres used an anonymised and standardised file to record data for their retrospective, consecutive case series. Patients resected from 1 January 2000 could be included and there was no requirement for a fixed reporting interval. In this study all patients operated with combined hepatic and biliary resection, with pCCA confirmed by postoperative pathology and with data on PSC status, were included in the analysis. Local ethical approval was obtained under local and institutional regulations for observational research. For analysis of the anonymised collected data, the Institutional Medical Ethics Committee of the Amsterdam University Medical Center waived the need for ethical approval or informed consent.

Outcome variables and clinicopathological data

The primary outcome variable was overall survival calculated from the date of surgery. The secondary outcome variables were disease-free survival, calculated from the surgery date, complications grade 3 or higher according to the Clavien-Dindo classification,[17] postoperative abscess or ascites requiring new drainage, postoperative liver failure grade B or C according to the International Study Group of Liver Surgery (ISGLS) criteria,[18] biliary leakage grade B or C as per the ISGLS criteria[19] and postoperative 90-day mortality. Clinicopathological variables were American Society of Anesthesiologists (ASA) classification of physical status, any episode of cholangitis (as defined in the DRAINAGE trial[20]) requiring additional biliary drainage between diagnosis and surgery, preoperative biliary drainage and drainage modality, the Bismuth-Corlette classification,[21] T-stage and N-status according to the seventh edition of the TNM Classification of Malignant Tumors,[22] tumour size, tumour-positive resection margin (R1), perineural tumour invasion (Pn1) and tumour grade according to the College of American Pathologists.[23]

Statistical analyses

Categorical variables were described as numbers and percentages. A comparison of proportions was made with the Chi-square or Fisher exact test as appropriate. Continuous variables were described as medians with interquartile ranges (IQRs). The

Mann–Whitney U test was used to compare distributions. Multivariate imputation of missing data was performed for covariates in the regression analysis.[24] Baseline characteristics and outcome variables were reported with unimputed data. Median follow-up time was calculated by the reverse Kaplan–Meier method. Statistical analysis was performed in SPSS Statistics v25 (IBM, New York, USA) and R (R 3.5.3, R Foundation for Statistical Computing; RStudio 1.1.463, RStudio Inc, Boston, USA).[25–29] Survival was analysed by Kaplan–Meier estimate and Cox regression. Survival curves were compared using the log-rank test for overall comparison and at three and five years with the c-log-log method for fixed time points.[29] Confidence intervals (CIs) for survival estimates were computed to take censoring and small sample size into account using the beta product confidence procedure for right-censored data.[28] The Cox proportional hazards assumption was assessed graphically and tested with scaled Schoenfeld residuals using the cox.zph function of the R Survival package, and variables with evidence of non-proportionality were modelled as time-dependent using the time-transform function with log time.[27] A two-sided p-value of $< .05$ was considered statistically significant.

Results

Study population

The flow chart for study inclusion of patients is presented in Fig. 1. Of 1524 patients resected for pCCA verified by histology between 1 January 2000 and 31 January 2020, PSC status was available for 1230 (81%). All patients with PSC pCCA had undergone combined hepatic and biliary resection. In the non-PSC pCCA group 102 patients underwent bile duct resection only and were excluded. In total, 1128 patients were included: 34 PSC pCCA patients (3.0%) and 1094 non-PSC pCCA patients (97.0%). The distribution of PSC pCCA patients per center is presented in Supplemental Fig. 1, with a median inclusion of one patient per center (IQR 0–2 patients). The median follow-up time was 50 months (IQR 20–89 months) for all patients, 61 months (IQR 25–69 months) for PSC pCCA patients and 50 months (IQR 20–89 months) for non-PSC pCCA patients.

Baseline characteristics

Patients with PSC-associated pCCA were younger than non-PSC pCCA patients, with a median age difference of 17 years ($p < .001$). Well-differentiated (grade 1) tumours were less frequent in PSC pCCA than in non-PSC pCCA (3% versus 16%, $p = .043$). The proportion of Bismuth-Corlette type IV tumours was similar in the PSC pCCA and non-PSC pCCA groups. Out of the 34 PSC pCCA patients, 22 had tumours 3 cm or larger and/or lymph node metastases. 11 PSC pCCA patients had tumours less than 3 cm, 5 of which were lymph node negative. Extended resections and preoperative portal vein embolisation were required more frequently in PSC pCCA. Preoperative biliary drainage by endoscopic retrograde cholangiography, alone (n = 14/34, 41%) or in combination with percutaneous drainage (n = 10/34, 29.5%), was more common in PSC. Table 1 summarises baseline clinical characteristics for PSC pCCA and non-PSC pCCA patients.

Postoperative complications

The complication rate (Clavien-Dindo grade 3 or higher) was significantly higher in PSC pCCA patients compared to non-PSC pCCA patients (71% versus 44%, $p = .003$). Postoperative abdominal drainage of abscess or ascites was more than twice as common in the PSC pCCA group. There were no statistically significant differences in the frequency of posthepatectomy liver failure, biliary leakage, or postoperative 90-day mortality rate

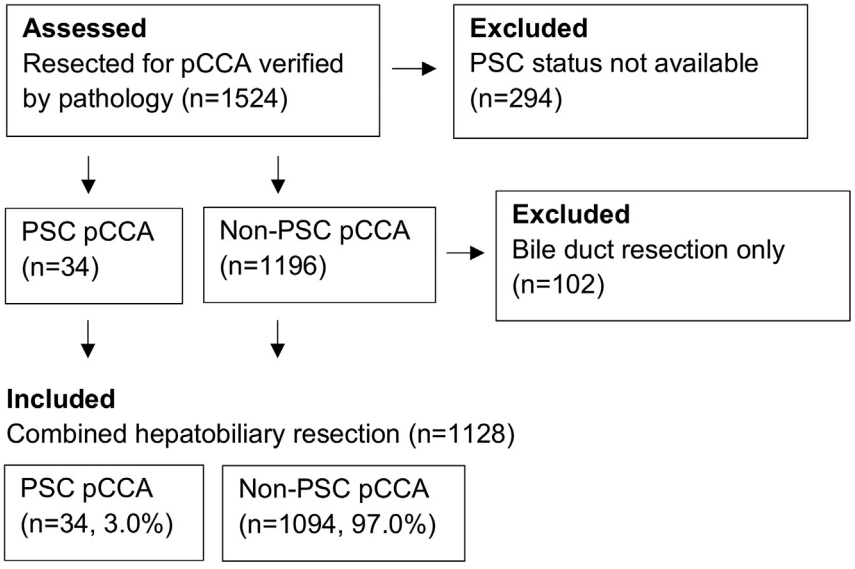

Figure 1 **Study flow chart illustrating the study population.** PSC: Primary sclerosing cholangitis; pCCA: perihilar cholangiocarcinoma

Table 1 Clinical characteristics of patients with PSC-associated pCCA and non-PSC pCCA

	Missing data n PSC/n Non-PSC	PSC n = 34	Non-PSC n = 1094	p-value
Age, years, median (IQR)	-/8	48 (36–63)***	65 (57–72)	<.001
Sex, male	–/–	23 (68%)	663 (61%)	.407
BMI, median (IQR)	5/215	23 (21–29)	25 (23–27)	.182
ASA class III or higher	1/64	11 (33%)	381 (37%)	.668
Preoperative ERC	-/2	24 (71%)*	563 (52%)	.029
Preoperative cholangitis	2/67	10 (31%)	247 (24%)	.350
Bismuth-Corlette IV	-/9	8 (24%)	242 (22%)	.866
PVE	–/–	11 (32%)*	177 (16%)	.013
Extended resection	–/–	20 (59%)*	425 (39%)	.019
Tumour size, cm, median (IQR)	9/192	3 (1.9–3.7)	2.5 (2.0–3.5)	.678
T-stage 3 or 4	2/16	13 (41%)	403 (37%)	.709
Lymph node positive	1/32	18 (55%)	445 (42%)	.148
Perineural invasion	2/146	27 (84%)	692 (73%)	.152
R1 margin status	-/10	11 (32%)	370 (34%)	.829
Moderate or poor tumour differentiation	1/71	32 (97%)*	859 (84%)	.043

Data expressed as n (%) unless otherwise stated.
pCCA: perihilar cholangiocarcinoma; PSC: primary sclerosing cholangitis; IQR: interquartile range; BMI: body mass index; ASA: American Society of Anesthesiologists physical status classification; Preoperative ERC: preoperative biliary drainage by endoscopic retrograde cholangiography (alone or in combination with percutaneous drainage); PVE: portal vein embolisation; R1: microscopically tumour-positive resection margin.
*p < .05 (Chi square test), ***p < .001 (Mann–Whitney U test).

between PSC pCCA and non-PSC pCCA patients. Postoperative complications are summarised in Table 2.

Survival

Median overall survival (95% CI) was 33 months (10–54 months) in PSC pCCA patients and 29 months (26–32 months) in non-PSC pCCA patients (log-rank p = .630). The 3- and 5-year overall survival (95% CI) was 39% (19–60%) and 19% (6–41%) in PSC pCCA patients and 43% (39–46%) and 27% (24–31%) in non-PSC pCCA patients (3-year overall survival p = .691, 5-year overall survival p = .393). Overall survival estimates for PSC pCCA patients and non-PSC pCCA patients are shown in Fig. 2A.

Disease-free survival estimates are displayed in Fig. 2B. Median disease-free survival (95% CI) was 20 months (11–38 months) in PSC pCCA patients and 22 months (19–25 months) in non-PSC pCCA patients (log-rank p = .741). The 3- and 5-year disease-free survival (95% CI) was 30% (12–54%) and 15% (2–38%) in PSC pCCA patients and 34% (29–38%) and 22% (18–27%) in non-PSC pCCA patients (3-year disease-free survival p = .728, 5-year disease-free survival p = .440). Registration of recurrence status was incomplete, with missing recurrence data for 39% of the included patients (missing data PSC pCCA n = 7, 21%; non-PSC pCCA n = 430, 39%).

Univariable survival analysis

Factors with a significant association with overall survival on univariable Cox regression analysis were male sex, ASA class ≥3, T-stage ≥ 3, lymph node metastasis, perineural invasion, moderate or poor tumour differentiation (grade ≥ 2), tumour-positive resection margin and portal vein embolisation. Results from univariable analyses are given in Table 3.

Table 2 Postoperative complications and mortality in patients with PSC-associated pCCA and non-PSC pCCA

	Missing data n PSC/n Non-PSC	PSC n = 34	Non-PSC n = 1094	p-value
Any complication Clavien-Dindo grade III or higher	-/4	24 (71%)*	484 (44%)	.003
Drained abscess/ascites	-/8	16 (47%)*	254 (23%)	.001
Liver failure ISGLS grade B/C	-/28	7 (21%)	176 (17%)	.530
Biliary leakage ISGLS grade B/C	-/27	9 (26%)	215 (20%)	.367
90-day mortality	–/–	4 (12%)	139 (13%)	1.000†

Data expressed as n (%) unless otherwise stated.
pCCA: perihilar cholangiocarcinoma; PSC: primary sclerosing cholangitis; ISGLS: International Study Group of Liver Surgery.
*p < .05 (Chi square test), † Fisher's exact test.

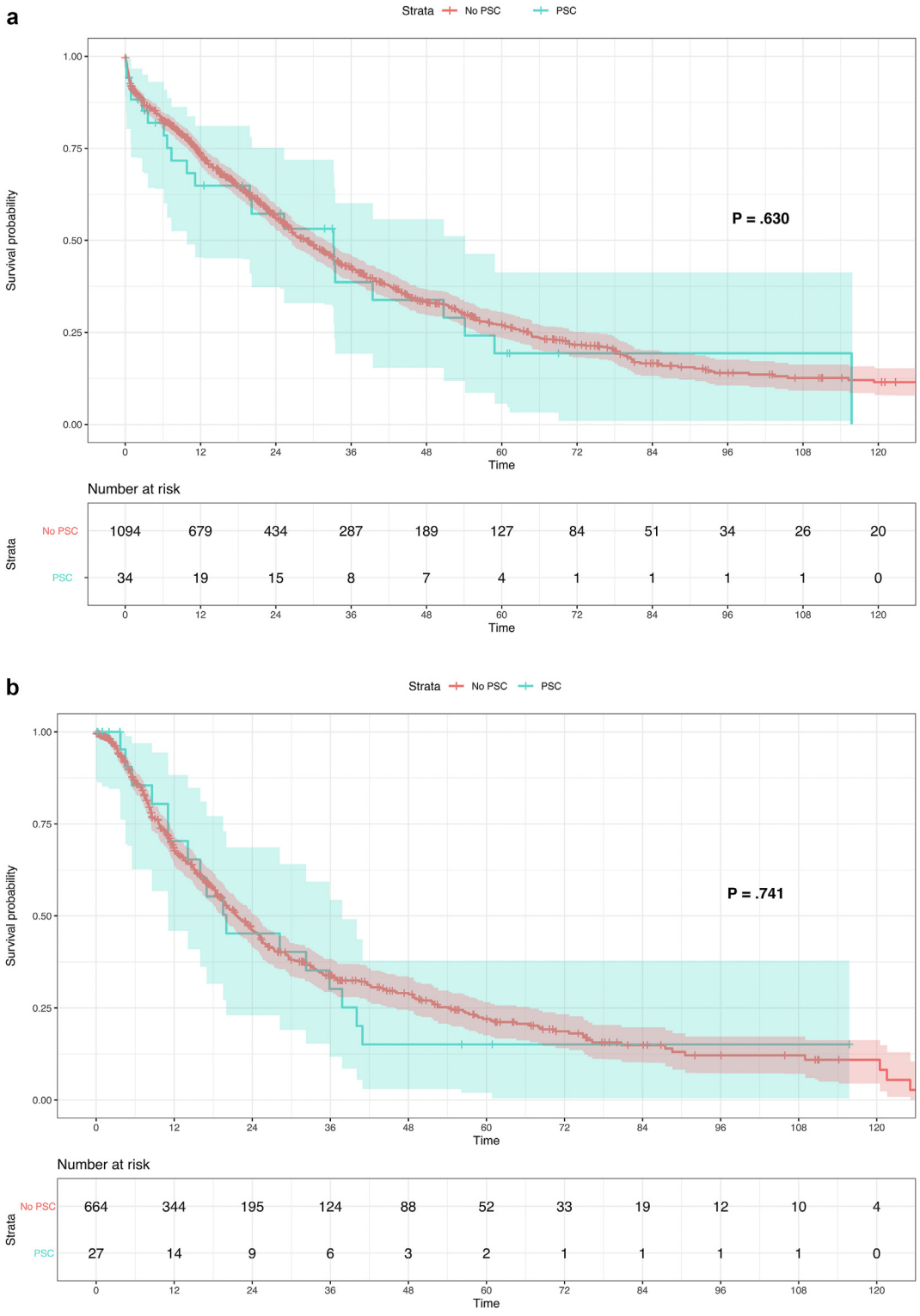

Figure 2 Overall survival (panel A) and disease-free survival (panel B) in PSC pCCA patients (blue) compared to non-PSC pCCA patients (red). Kaplan–Meier estimates with 95% confidence intervals (shaded bands). Time in months. Survival curves compared using the log-rank test. pCCA: perihilar cholangiocarcinoma; PSC: primary sclerosing cholangitis

Table 3 Univariable and multivariable Cox regression analyses of prognostic factors for overall survival after resection

	Univariable analysis HR (95% CI)	p-value univariable	Multivariable analysis: PSC, age HR (95% CI)	Multivariable analysis: PSC, age, sex, ASA HR (95% CI)	Multivariable analysis: pre- and post-operative factors HR (95% CI)
Age (years) [time-dep]	1.00 (1.00–1.00)	.557	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Sex (male)	1.31* (1.12–1.53)	<.001		1.26* (1.08–1.48)	1.30* (1.11–1.52)
ASA class III or higher	1.44* (1.24–1.68)	<.001		1.45* (1.24–1.70)	1.38* (1.18–1.62)
PSC	1.11 (.73–1.70)	.632	1.08 (.70–1.67)	1.02 (.66–1.57)	.83 (.53–1.29)
Portal vein embolisation	1.23* (1.01–1.51)	.038			1.14 (.93–1.40)
Extended resection	1.16 (.99–1.35)	.062			1.13 (.97–1.33)
T-stage 3 or 4	1.35* (1.16–1.57)	<.001			1.15 (.98–1.34)
Lymph node positive	1.79* (1.54–2.08)	<.001			1.63* (1.39–1.91)
Perineural invasion	1.61* (1.34–1.93)	<.001			1.37* (1.14–1.66)
Moderate or poor tumour differentiation [time-dep]	1.14* (1.06–1.23)	<.001			1.14* (1.05–1.22)
R1 margin status	1.67* (1.43–1.95)	<.001			1.50* (1.28–1.76)

HR: hazard ratio; CI: confidence interval; ASA: American Society of Anesthesiologists physical status classification; PSC: primary sclerosing cholangitis; R1: microscopically tumour-positive resection margin; time-dep: time-dependent variable.
*p < .05.

Multivariable survival analysis

Factors significantly associated with overall survival on multivariable analysis were male sex, ASA class ≥3, lymph node metastasis, perineural invasion, moderate or poor tumour differentiation (grade ≥ 2) and tumour-positive resection margin. Results from multivariable Cox regression analyses are given in Table 3. Underlying PSC was not prognostic for overall survival on multivariable analysis (age-adjusted hazard ratio 1.08, 95% CI .70–1.67). Also presented in Table 3 are adjusted hazard ratios from a preoperative prognostic model (PSC, age, sex, ASA), and a multivariable model including preoperative factors, surgical factors (portal vein embolisation, extended resection, R1) and postoperatively available tumour characteristics (T-stage, N-status, Pn1, tumour differentiation).

Discussion

In this large international multicentre study reporting the largest series of resected PSC pCCA patients to date to our knowledge, median overall survival after resection for PSC-associated pCCA was 33 months and 3-year overall survival was 39% (95% CI 19–60%). For non-PSC pCCA patients median overall survival was 29 months and 3-year overall survival was 43% (95% CI 39–46%). These findings contrast with earlier descriptions of a dismal prognosis for PSC pCCA patients even with R0-resection,[11,12,14] compared to non-PSC pCCA patients.

Comparing prognostic clinicopathological factors, patients with underlying PSC had a lower rate of well-differentiated tumours. This difference in tumour grade may adversely affect long-term survival in PSC pCCA patients. PSC pCCA patients, however, did not have tumours of more advanced T-stage or a significantly higher rate of lymph node metastasis compared to non-PSC pCCA patients. Possible explanations for the similar tumour stage could be patient selection criteria for resection surgery and surveillance protocols for malignancy in PSC, allowing diagnosis of cholangiocarcinoma at less advanced stages compared to earlier series.

The rate of postoperative complications was high after resection in PSC patients and increased compared to non-PSC patients, even if PSC patients on average were markedly younger when operated for pCCA. Comparing specific complications, postoperative drainage of abscess or ascites was more than twice as common in the PSC pCCA group. In contrast, rates of post-hepatectomy liver failure, biliary leakage and 90-day mortality did not differ significantly. Pre-existing hepatobiliary disease and an altered immune response (due to immunosuppression or disease-specific immune dysfunction) are PSC-specific factors that can contribute to postoperative morbidity. PSC patients with biliary stricture often repeatedly undergo diagnostic and therapeutic endoscopic retrograde cholangiography, possibly increasing the risk of bacterial biliary contamination and post-operative infectious complications in these patients.

Postoperative mortality was comparable in the PSC pCCA (12%) and non-PSC pCCA (13%) groups. The mortality in the whole cohort (12.7%) was similar to what has been reported (10–14%) in other Western studies.[4,30–34] The considerable risk of postoperative mortality after combined hepatobiliary resection for pCCA reaffirms the importance of adequate preoperative biliary drainage, preoperative portal vein embolisation when indicated and a careful assessment of both volume and function of the future liver remnant as part of a preoperative risk evaluation.[35,36]

The proportion of patients who underwent resection for PSC pCCA in this cohort was higher than in the resection group of the US Extrahepatic Biliary Malignancy Consortium (USEBMC) cohort (3.0% versus 1.6%).[4] This discrepancy could reflect both geographical differences of PSC prevalence, which varies considerably within Europe and the US,[11,37] and possible differences in the application of the Mayo protocol for transplantation in PSC pCCA. The poor 5-year overall survival of 19% in this cohort, compared to results for liver transplantation, indicates how PSC pCCA patients could benefit from neoadjuvant treatment and transplantation if eligible according to the Mayo protocol criteria.[4,14] While incomplete, available tumour size data shows that whereas a majority of PSC pCCA patients in this study had tumours 3 cm or above and/or lymph node metastases, precluding transplantation, some patients could potentially have been eligible for transplantation within Mayo criteria.

Strengths of the current study include the international multicentre design and large size of the cohort, in which patients were characterised by clinicopathological and surgical factors and followed postoperatively for a median time of 50 months. The cohort of resected pCCA patients reported here is larger than other recently reported multicentre pCCA case series.[9,30,38,39] The PSC pCCA group represents the largest series of resected PSC pCCA patients reported to date to our knowledge. This series of PSC pCCA patients is also larger than several previously reported PSC pCCA groups in recent multicentre publications on liver transplantation in pCCA.[4,40,41] All in all, a systematic meta-analysis included 180 transplanted PSC pCCA patients from 13 studies reported internationally 2000–2019.[42]

Yet, as PSC is a rare disease, the sample size of the PSC pCCA group was small, limiting statistical power. Other limitations include the long study period and the retrospective cohort study design. The difference in median follow up time between non-PSC patients and PSC patients may also skew results. Moreover, data on preoperative liver function, fibrosis grade, presence of portal hypertension and surveillance in PSC were lacking, and missing data on PSC status reduced the set of patients available for analysis. The cohort consisted of resected pCCA patients, thus lacking data on selection for surgery and also precluding any comparison between outcomes for resection and transplantation. The time of recurrence was incompletely reported, decreasing the power and precision of the estimates of disease-free survival.

In conclusion, this study reports unique multicentre data on prognostic factors and outcomes after resection for PSC-associated pCCA. The median overall survival of PSC pCCA patients was similar to that of non-PSC pCCA patients. PSC pCCA patients have a higher risk of postoperative complications, which underscores the importance of meticulous preoperative risk evaluation and treatment in PSC.

Acknowledgements

Perihilar Cholangiocarcinoma Collaboration Group: Andreou A, Bartsch F, Benzing C, Buettner S, Capobianco I, Charco R, de Reuver PR, de Savornin Lohman E, Dejong CHC, Efanov M, Erdmann JI, Franken LC, Giglio MC, Gomez-Gavara C, Hagendoorn J, Heid F, IJzermans JNM, Kazemier G, Maithel SK, Malago M, Malik HZ, Molenaar QI, Muiesan P, Nooijen LE, Nota CLM, Olde Damink SWM, Pratschke J, Quinn LM, Ratti F, Ravaioli M, Roberts KJ, Rolinger J, Ruzzenente A, Schadde E, Schmelzle M, Serenari M, Sultana A, van Laarhoven S, van Vugt JLA, Zonderhuis BM.

The authors would like to acknowledge the ERN RARE-LIVER European Reference Network on Hepatological Diseases and the EURO-CHOLANGIO-NET European Cholangiocarcinoma Network.

Funding

Hannes Jansson was supported by grants from the Royal Swedish Academy of Sciences and Region Stockholm. Ernesto Sparrelid was supported by grants from the Bengt Ihre Foundation, the Center for Innovative Medicine at Karolinska Institutet and Region Stockholm. The funding sources had no involvement in the design or conduct of the study, the writing of the report or the decision to submit the article for publication.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.04.011.

