Original paper

Intrahepatic cholangiocarcinoma as an aetiologically distinct type of biliary cancer

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Abstract

Introduction: Cholangiocarcinoma (CCA) comprises a heterogeneous group of biliary cancers showing different clinical characteristics. Intrahepatic cholangiocarcinoma (iCCA) is rare disease that is clinically different from other biliary malignancies.
Aim of the research: The purpose of this study was to provide clinical characteristics of iCCA in comparison to perihilar CCA (pCCA), extrahepatic CCA (eCCA), gallbladder cancer (gCA), and ampullary cancer (aCA).
Material and methods: A total of 104 patients aged 36 to 89 years with histologically confirmed CCA, hospitalised in the tertiary gastroenterological centre between 2018 and 2022, were retrospectively analysed in terms of demographic characteristics, clinical presentation, and survival.
Results: Patients with iCCA (n = 18) were younger in comparison to patients with other biliary cancers (62.8 ±10.9 vs. 70.1 ±10.2 years; $p < 0.05$), had significantly higher BMI (27.0 ±4.9 vs. 24.5 ±3.6 kg/m^2; $p < 0.05$), and higher prevalence of liver steatosis (22.2% vs. 7.05%; $p < 0.05$). Weight loss and right epigastric pain were leading signs of iCCA, but low intensity of pain (median NRS 2.0 vs. 4.5; $p < 0.05$) and low incidence of jaundice (22.2% vs. 61.8%; $p < 0.05$) were responsible for delayed diagnosis of liver tumour, which at initial presentation was large (63.2 ±29.2 mm), and commonly associated with metastases to regional lymph nodes or peritoneum (94.4%).
Conclusions: Intrahepatic CCA is a distinct disease among other biliary cancers, favourably arising in steatotic liver in overweight patients. The prognosis in iCCA is poor due to delayed diagnosis resulting from insidious tumour growth.

Introduction

Cholangiocarcinoma (CCA) comprises a heterogeneous group of neoplasms arising from biliary epithelium or periductal glands, which are, depending on their anatomical localisation, divided into intrahepatic, perihilar, and extrahepatic types [1, 2]. Other variants of CCA are gallbladder cancer (gCA) and ampullary cancer (aCA).

Epidemiological estimates of CCA vary greatly by geographical region. In West European countries CCA accounts for about 3% of all gastrointestinal cancers, with incidence rates ranging from 0.3 to 6.0 cases per 100,000 inhabitants [1, 3–6]. According to the White Book published by United European Gastroenterology in 44 member countries combined, age-standardised incidence and mortality rates in patients with biliary tract and gallbladder cancers (ICD-10: C23 and C24) have decreased between 2000 and 2019 by around 24% and 28%, respectively; however, in the same period the incident cases and deaths increased due to general prolongation of life span. In Poland an epidemiology report by the National Oncology Institute claims that CCA belongs to the group of rare neoplasm, responsible for 1% of all oncological diseases [7].

Intrahepatic CCA (iCCA) is the second most common primary malignant liver tumour, after hepatocellular carcinoma [1, 3–5]. Epidemiological accounts of iCCA are complicated by the fact that most cancer registries combine this tumour with other hepatobiliary malignancies [8, 9]. In Western countries iCCA is responsible for 10–20% of biliary cancers, and in Poland this cancer represents 14% of CCA cases, far behind gallbladder or perihilar cancer [2, 7]. Intrahepatic CCA is distinct from among other CCAs with respect to diagnostic and therapeutic approaches. Although the prevalence of extrahepatic and gallbladder CCAs have declined in recent decades, the prevalence of iCCA is rising, and the risk factors associated with development of this cancer and its natural history are poorly recognised.

Aim of the research

The purpose of this study was to characterise iCCA with respect to risk factors, clinical presenta-

tion, and prognosis in comparison to other biliary malignancies.

Material and methods

Patients

In this retrospective study, patients hospitalised in the tertiary gastroenterology centre from July 2018 to March 2022 with cholestasis and histologically confirmed biliary cancer were enrolled. The exclusion criteria were concurrent extrabiliary neoplasm or pregnancy. Clinical and demographic data derived from medical documentation were collected. The patients were allocated into one of five groups according to final diagnosis: iCCA, perihilar biliary cancer (pCCA), extrahepatic cholangiocarcinoma (eCCA), gCA, and aCA. The patient follow-up was completed on 31 August 2022 or on the day of the patient's death.

Data collection

Data were derived from hospital electronic records and included medical interview, physical examination, laboratory results, reports of pharmacological or endoscopic therapies, and decisions of local Oncology Councils on further management. The severity of pain assessment ranged from 0 (no pain) to 10 (strong pain) according to the Numeric Rating Scale (NRS). The general physical condition and quality of life was assessed by the Zubrod scale [10] modified in 1982 by the ECOG (Eastern Cooperative Oncology Group).

Imaging data (ultrasound, computed tomography, magnetic resonance, endoscopic retrograde cholangiopancreatography) included anatomical site of cancer, size of the tumour, presence of ascites, infiltration of large vessels, and liver or peritoneal metastases. The pCCA was specified by Bismuth-Corlette classification [11]. Histological reports provided information on cancer grading, microvascular infiltration, and invasion of lymph nodes.

Statistical analysis

Baseline demographics and risk factors were summarised using descriptive statistics. The qualitative variables were presented as *n* (%). For variables showing normal distribution, the means and standard deviations were calculated, and for variables deviating from normal distribution, the median values were chosen. The distribution of quantitative variables was tested using the Shapiro-Wilk test. One-way ANOVA (one-way analysis of variance) or the unpaired *t* test was applied to check the differences between means of the studied groups. In the case of variables that did not meet the required assumptions, the Kruskal-Wallis one-way ANOVA or the *U* Mann-Whitney test was used. To define the relationships between variables, analyses of correlations and regressions were conducted. The χ^2 test with Yates correction was used to evaluate the relationships between groups and qualitative variables. A p level of less than 0.05 was considered statistically significant. All statistical analyses were performed with TIBCO Statistica, version 13.3.0, TIBCO Software Inc., Palo Alto, CA, USA.

Results

The characteristics of 104 patients aged 36 to 89 years (mean: 68.7 ±10.8 years) enrolled in the study are shown in Table 1. The patients with iCCA were significantly younger and had significantly higher body mass index (BMI) than patients with other biliary cancers. The causes of hospitalisation were symptomatic disease and/or finding the tumour or dilated biliary ducts in imaging diagnostics.

At initial presentation, jaundice was present in 22.2% of patients with iCCA, significantly less frequently than in other types of CCA ($p < 0.05$). Patients with iCCA commonly reported abdominal pain; however, the severity of pain was statistically smaller than in other biliary cancers. The duration of right hypochondrium pain/discomfort reported by iCCA patients was 13.8 ±11.9 weeks, which was the greatest among biliary cancers ($p < 0.01$).

Weight loss was reported by 55.5% of iCCA patients, and within 6 months it was 10.1 ±7.1 kg. The physical performance of patients with different types of biliary cancers is shown in Table 1. No patient showed signs of circulatory or respiratory failure during hospitalisation, and no patient had signs of liver cirrhosis or had been diagnosed with primary sclerosing cholangitis.

Criteria for overweight and obesity were fulfilled in iCCA patients in 55.6% and 16.7%, respectively, significantly more often than in other types of biliary cancers. BMI greater or equal to 25 kg/m^2 was found in 77.8% of patients with iCCA, and fatty liver was diagnosed in 22.2% of these patients, while in other types of biliary cancers, diagnosis of fatty liver ranged from 4% to 9.5%. The main metabolic comorbidities are presented in Table 1. In the iCCA group one woman underwent surgery because of breast cancer. The highest frequency of coexistent or past oncological diseases was found in patients with pCCA ($p < 0.05$).

Basic laboratory data in patients with different biliary cancers are presented in Table 2. The plasma levels of bilirubin, alanine aminotransferase, and cholestatic enzymes were significantly lower in iCCA than in other groups. There was mild anaemia in all groups, and the white blood cell count (WBC) was significantly higher in iCCA and gCA than in other patients. The C-reactive protein (CRP) serum level was elevated in all groups of patients, but in iCCA it was significantly lower than in pCCA, eCCA, and aCA ($p < 0.05$). Cancer antigen 19.9 (Ca19.9) levels were markedly elevated in all groups of patients apart from aCA, with the highest level in patients with gCA ($p < 0.05$).

Table 1. Demographic and clinical characteristics of patients with different types of biliary cancer

Variable, unit	Type of biliary cancer				
	iCCA	pCCA	eCCA	gCA	aCA
Number of patients	18	21	22	18	25
Age [years], mean ± SD	62.8 ±10.9[a]	67.9 ±10.3	69.8 ±10.9	67.2 ±9.1	74.0 ±9.6
Sex (male/female), *n*	7/11	9/12	12/10	7/11	9/16
Working/pensionary, *n*	5/13	4/17	4/18	3/15	3/22
Social status (medium-to-high/low), *n*	15/3	18/3	20/2	18/0	22/3
Jaundice, *n* (%)	4 (22.2)[a]	12 (57.1)	15 (68.2)	12 (66.6)	14 (56.0)
Abdominal pain, *n* (%)	11 (61.1)	10 (47.6)	10 (45.5)	13 (72.2)	13 (52.0)
NRS score, median and lower-upper quartiles	2.0[b] 2–8	5.0 3–6	4.0 2–6	4.0 2–5	5.0 2–7
Duration before diagnosis [weeks], mean ± SD	13.8 ±11.9[b]	6.5 ±6.3	6.2 ±5.7	9.4 ±10.9	6.9 ±8.3
ECOG 0-1, %	15 (83.3)	18 (85.7)	13 (59.1)	12 (66.7)	19 (76.0)
BMI [kg/m^2], mean ± SD	27.0 ±4.9[a]	23.9 ±3.5	24.2 ±2.6	25.5 ±3.3	24.7 ±4.5
Overweight, *n* (%)	14 (77.8)[a]	7 (33.3)	9 (40.9)	10 (55.6)	15 (60.0)
Fatty liver disease, *n* (%)	4 (22.2)[a]	2 (9.5)	2 (9.1)	1 (5.6)	1 (4.0)
Weight loss before diagnosis, % kg/6 months and mean ± SD	55.5% 10.1 ± 7.1	52.4% 7.0 ± 2.8	54.5% 11.8 ± 6.2[a]	61.1% 10.3 ± 10.4	36.0% 9.6 ± 3.3
Type 2 diabetes, *n* (%)	5 (27.8)	6 (28.6)	7 (31.8)	4 (22.2)	7 (28.0)
Arterial hypertension, *n* (%)	13 (72.2)	18 (85.7)	13 (59.1)	11 (61.1)	16 (64.0)
Hyperlipidaemia, *n* (%)	5 (27.8)	9 (42.9)	9 (40.1)	5 (27.8)	5 (20.0)[a]
Gallbladder stones or past cholecystectomy, *n* (%)	3 (16.7)	9 (42.9)	12 (54.5)	5 (27.8)	9 (36.0)
Active/past smokers, *n* (%)	6 (33.3)	9 (42.9)	4 (18.2)	3 (16.7)	7 (28.0)
Alcohol abuse, *n* (%)	4 (22.2)	4 (19.0)	4 (18.2)	2 (11.1)	4 (16.0)
Oncological history, *n* (%)	1 (5.6)	8 (38.1)[a]	1 (4.5)	0	5 (20.0)
First-line family history of cancer, *n* (%)	7 (38.8)	8 (38.1)	4 (18.2)	6 (33.3)	9 (36.0)
Metastases (liver, lymph nodes, peritoneum), *n* (%)	17 (94.4)	21 (100.0)	19 (86.4)	18 (100.0)	12 (48.0)
Specific treatment: (surgery, chemotherapy, radiotherapy), *n* (%)	10 (55.6)	2 (9.5)	13 (59.1)	6 (33.3)	15 (60.0)
Mean survival [months], mean ± SD	3.4 ±1.8[a]	4.1 ±2.3	4.1 ±1.9	2.4 ±1.3	7.5 ±3.2
Annual survival, %	29	5	20	13	38

[a]p < 0.05; [b]p < 0.01; BMI – body mass index; NRS – Numerous Rating Scale; ECOG – Eastern Cooperative Oncology Group scale (grade 0 signifies full activity with ability to carry on all pre-disease performances without restrictions, grade 1 – patient is restricted in physically strenuous activity but able to carry out work of a light or sedentary nature, grade 2 – ambulatory patients are capable of all self-care but unable to carry out any work activities or up and about more than 50% of waking hours, grade 3 – patient is capable of only limited self-care and is confined to bed or chair more than 50% of waking hours, grade 4 – patient is completely disabled and cannot perform any self-care - totally confined to bed or chair, grade 5 – denotes the disease related death).

Intrahepatic CCA was a single tumour located in the right hepatic lobe in 61% of cases, with a mean tumour size of 63.2 ±29.2 mm, and invasion of hepatic hilar or periportal lymph nodes reported in imaging or histopathological examinations in 72.2% of cases. Metastases to peritoneum were found in 22.2% of iCCA patients. Five patients with iCCA (27.7%) underwent endoscopic biliary stenting because of intraductal growth of the tumour with dilatation of intrahepatic biliary ducts. In iCCA patients the surgical resection was undertaken in 27.8% of patients, 27.8% were treated with chemotherapy (gemcitabine or gemcitabine with cisplatin), and palliative care was used in 44.6% of patients. In iCCA, 55.5% of patients died

Table 2. Laboratory data in patients with different biliary cancers

Variable, unit, reference values	Type of biliary cancer				
	iCCA	pCCA	eCCA	gCA	aCA
Albumin [g/dl] Ref. 3.5–5.2	4.2 ±0.5	4.2 ±0.2	2.6 ±0.3	3.2 ±0.9	3.3 ±0.5[a]
Prothrombin index, %, Ref. 80–120	70.3 ±22.1	76.8 ±22.8	75.5 ±24.1	80.6 ±12.6	74.5 ±15.9
Bilirubin [mg/dl] Ref. < 1.2	4.7 ±8.7[b]	11.1 ±11.4	11.9 ±12.8	14.3 ±10.1	8.2 ±6.4
ALT [IU/l] Ref. < 35	118 ±175[b]	148 ±96	165 ±175	222 ±252	148 ±118
AST [IU/l] Ref. < 35	138 ±170[a]	164 ±111	159 ±161	179 ±172	143 ±149
Alkaline phosphatase [IU/l] Ref. < 104	453 ±506[a]	876 ±682	658 ±505	787 ±636	491 ±362
GGT [IU/l] Ref. < 40	429 ±627[b]	1131 ±749[a]	893 ±783	798 ±642	618 ±473
Glucose [mg/dl] Ref. < 99.0	94.4 ±47.1	97.8 ±45.5	109 ±64.1	84.5 ±33.3	105 ±50.2
Creatinine [mg/dl] Ref. 0.51–0.95	0.9 ±0.3	0.9 ±0.2	0.9 ±0.4	1.0 ±0.3	1.1 ±0.8
CRP [mg/l] Ref. < 5.0	39.1 ±33.4	84.2 ±86.2[a]	64.6 ±61.6[a]	60.8 ±80.7	56.3 ±55.3[a]
Natrium [mmol/l] Ref. 136–145	137 ±5.5[b]	134 ±4.7	135 ±4.9	135 ±4.1	137 ±2.9
Haemoglobin [g/dl] Ref. 12.5–16.0	12.3 ±1.7	11.9 ±1.6	12.2 ±2.1	11.5 ±1.4	11.3 ±1.3[a]
RBC [10^6/mm^3] Ref. 3.7–5.0 for women, 4.2–5.7 for men	4.2 ±0.6[a]	3.8 ±0.6	3.9 ±0.7	3.8 ±0.6	3.7 ±0.5[a]
WBC [10^3/mm^3] Ref. 4.0–10.0	11.7 ±7.2[a]	9.6 ±3.3	10.3 ±4.9	11.8 ±5.6[a]	9.4 ±5.9
Neutrophils [10^3/mm^3] Ref. 2.5–5.0	8.1 ±6.2	7.1 ±3.6	10.5 ±16.9	8.7 ±5.4	7.2 ±6.7
PLT [10^3/mm^3] Ref. 130–400	321 ±138	281 ±122	288 ±113	322 ±143	327 ±163
AFP [ng/ml] Ref. < 7.0	3.8 ±1.6	5.8 ±5.6	3.3 ±1.6	3.9 ±0.9	4.2 ±1.0
CEA* [ng/ml] median, lower–upper quartiles Ref. < 5.2 in non–smokers, < 6.5 in smokers	5.24 1.50–25.9	4.35 2.89–12.4	5.14 2.15–14.2	6.28 6.09–20.4	4.02 2.38–6.4
Ca19.9* [IU/ml] median; lower–upper quartiles Ref. < 27.0	232 22–4593	594 267–9410	485 116–2621	1936[a] 125–5451	72 23.5–577

**All data except CEA and Ca19.9 are expressed as mean ± standard deviation. [a]p < 0.05; [b]p < 0.001; ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – gamma–glutamyl transferase, CRP – C–reactive protein, RBC – red blood count, WBC – white blood count, PLT – platelet count, AFP – alpha–fetoprotein, CEA – carcinoembryonic antigen, Ca19.9 – cancer antigen 19.9.*

before the end of observation, and the mean survival time in this group was 3.4 ±1.8 months, being significantly shorter than others, except gCA ($p < 0.05$). Ampullary CA was associated with highest rate of surgical resections and better survival than iCCA.

Discussion

In Europe, a noticeable increase in mortality due to iCCA over the last 10 years has been reported in both men and women [12]. CCAs comprise a het-

erogeneous group of cancers arising from the whole length of the biliary tract, which may differ according to aetiology, clinical presentation, and prognosis [13]. Potential risk factors for CCA are chronic inflammation of biliary ducts, biliary stone disease, unhealthy diet, smoking, and alcohol use. This single-centre study performed in a tertiary gastroenterology unit examined differences in clinical data between iCCA and other biliary cancers.

In our study, the mean age of patients at the time of iCCA diagnosis was 62.8 years, and on average it was 7 years lower than in other CCA types. Jaundice was the first presentation of disease in 22.2% of patients, which was significantly less often than in other biliary cancers. Lower prevalence of jaundice, and lower levels of bilirubin and hepatic enzymes reflecting both impaired bile flow and hepatocytic injury could be expected as iCCA arises within the liver, with moderate or absent dilatation of intrahepatic biliary ducts. Moreover, CRP levels were elevated but to a significantly lower level than in other biliary cancers. Increased CRP levels in patients with malignant biliary obstruction may be the result of bacterial or chemical cholangitis due to high concentration of toxic bile acids. In this respect, the decision on endoscopic intervention in patients with iCCA may be challenging because only a minority of them would benefit in terms of amelioration of liver function tests [14].

The leading signs of iCCA were right hypochondrium pain and weight loss; however, these symptoms differed significantly from other biliary cancers. Intensity of pain measured by NRS was significantly inferior to that reported by patients with other types of CCA and was mostly felt as discomfort tolerated for a significantly longer period of time in comparison to patients with other biliary cancers. Paying little attention to the symptoms by patients with iCCA could also be explained by relatively good physical condition evidenced by ECOG classification despite weight loss amounting on average to 10 kg. In a meta-analysis of 25 primary care studies, the unexplained weight loss showed specificity from 92% to 99% for several malignancies, including biliary cancer [15]. Owing to mild expression of alarming signs, the diagnosis of iCCA was greatly delayed, resulting in high incidence of metastases to perihilar lymphatic nodes and/or peritoneum. Mean survival of iCCA patients was significantly worse than in patients with extrahepatic biliary cancers and similar to gallbladder cancer, which is believed to be the most aggressive type of CCA [16, 17]. Consequently, only 55.6% of patients with iCCA were found to be eligible for specific therapy based on chemotherapy or radiotherapy. In Poland almost 50% patients with biliary cancers are diagnosed in the disseminated stage [7]. Although Ca19.9 plasma levels were elevated in all types of CCA, in patients with iCCA its median concentration was within reference values and was significantly lower than in gall bladder cancer. A high Ca19.9 level is deemed an independent prognostic factor in biliary cancers associated with extrahepatic spread, but also the degree of bile flow impairment, which was lower in iCCA compared to extrahepatic bile obstruction [18].

Recent studies indicated that iCCA occur with a background of chronic liver disease, and in the European Network for the Study of Cholangiocarcinoma (ENS-CCA) 12.6% of registered cases of iCCA developed in cirrhotic liver [6]. In our study no patient showed signs of liver cirrhosis. The most common chronic liver diseases are metabolic dysfunction associated steatotic liver disease (MASLD), alcohol-related liver disease, and viral hepatitis C or B. In the iCCA group there was no patient with HCV or HBV infection, and the percentage of patients with alcohol abuse was not different from those with other CCA types. Among patients with iCCA the incidence of overweight was higher than in patients with other biliary cancers, despite striking weight loss related to the tumour. In 77.8% of patients with iCCA the BMI was greater than or equal to 25 kg/m^2. It may therefore be assumed that before development of iCCA most of these patients were obese. In accordance, the finding of liver steatosis in imaging methods was significantly more frequent in iCCA patients than in other biliary cancers. Steatotic liver was found in 22.2% of patients with iCCA, while in other types of biliary cancer the diagnosis of fatty liver ranged from 4% to 9.5%. These data suggest that liver steatosis and obesity are risk factors for iCCA, and survival in in this cancer could depend not only on tumour advancement but also progression of chronic liver disease. The pandemic of obesity that has grown in western Europe rapidly since the 1970s may explain the rise in prevalence of iCCA [19–21]. Cardiometabolic risk factors typical for MASLD such as diabetes, hyperlipidaemia, or arterial hypertension were not different in iCCA to other biliary malignancies. The hyperlipidaemia may be an inappropriate clue in the diagnosis of MASLD in iCCA because cholestasis itself is responsible for elevated cholesterol levels. Type 2 diabetes was diagnosed in 22.2% to 31.8% of patients with different biliary cancers, which is greater than in the adult general population in Poland [22]. It should be noted that the limitations of this study were the low number of patients with iCCA undergoing retrospective analysis and the single-centre experience; larger studies are needed to confirm these results.

Conclusions

Steatotic liver in overweight patients is a risk factor for development of iCCA. Owing to subtle hepatic symptoms, iCCA is diagnosed at an advanced stage, when a significant portion of patients fail to receive cancer-specific therapies. The increasing incidence of iCCA, which is the second most common primary

liver cancer, merits special diagnostic attention. This study showed that in the population aged 50 years and older right hypochondrium discomfort associated with weight loss should alert to the possibility of iCCA.

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Ethical approval

The study was designed to conform to the ethical guidelines of the Declaration of Helsinki (1989).

Conflict of interest

The authors declare no conflict of interest.

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