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Extracapsular tumor spread does not influence survival outcomes in resected N1-patients with intrahepatic cholangiocarcinoma– a retrospectively controlled cohort study

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ABSTRACT

Background: Extracapsular tumor spread (ECS) in lymph nodes is a known predictor of recurrence and decreased survival across various malignancies, including breast and head and neck cancers. However, its prognostic value in patients with intrahepatic cholangiocarcinoma (iCCA) undergoing curative surgery has not yet been explored.
Methods: A retrospective cohort study was conducted, including all patients with lymph node-positive disease (N1) who underwent curative resection for iCCA between 2008 and November 2023. Patients were followed up for at least one year postoperatively. Cases with ECS-positive lymph nodes (N1/ECS+) were compared to those without extracapsular tumor infiltration (N1/ECS-). Statistical analyses included the T-test for continuous variables and the Chi-square test for categorical variables. Survival outcomes were evaluated using the Kaplan-Meier method.
Results: 70 patients with N1 disease following potentially curative resection were included. Baseline characteristics were comparable between groups (N1/ECS + n = 30, N1/ECS- n = 40), with no significant differences in age (p = 0.853), resection type (p = 0.511), T-stage (p = 0.785), resection margins (p = 0.687) or the number of tumor-positive lymph nodes (p = 0.052). The median overall survival (OS) was 17.2 months in the N1/ECS + group and 17.3 months in the N1/ECS- group (p = 0.466). Similarly, recurrence-free survival (RFS) was not significantly different, with a median of 4.4 months for N1/ECS + patients versus 7.7 months for N1/ECS- patients (p = 0.335).
Conclusion: Extracapsular tumor spread in lymph nodes was not associated with significant differences in overall or recurrence-free survival in patients with intrahepatic cholangiocarcinoma undergoing curative resection. Based on these findings, ECS does not appear to serve as a prognostic predictor of outcomes in this population.

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1. Introduction

Intrahepatic cholangiocarcinoma (iCCA) is a rare and aggressive primary liver malignancy, with a rising incidence globally [1,2].

Surgical resection remains the only potentially curative treatment; however, prognosis remains poor, with 5-year survival rates ranging from 21.4 % to 40 %. [3,4]. Recent advances in iCCA management have been primarily driven by novel immunotherapeutic approaches, such as the PD-L1 inhibitor durvalumab, which have demonstrated improved overall survival in patients with advanced disease [5].

In the era of personalized therapies, the identification of reliable prognostic markers capable of stratifying patients by recurrence risk following curative-intent surgery is of paramount importance. Such markers could inform post-operative surveillance protocols and guide decisions regarding the use of adjuvant systemic therapies. Extracapsular tumor spread (ECS) in lymph nodes has emerged as a well-established adverse prognostic factor in various malignancies, including breast and head and neck cancers [6,7].

However, to date, there has been a paucity of data evaluating the prognostic relevance of ECS in patients with iCCA undergoing curative resection. A comprehensive review of the literature (detailed in the Methods section and Appendix A) did not identify any prior studies specifically addressing this question. To address this gap, we conducted a retrospective cohort study of patients with pathologically confirmed lymph node-positive (N1) iCCA who underwent curative resection, utilizing data from one of the largest Western surgical series of cholangiocarcinoma. This study aimed to evaluate the prognostic impact of ECS in this patient population.

2. Methods

2.1. Literature review

A systematic literature review was conducted using the PubMed database to identify studies relevant to the prognostic significance of extracapsular tumor spread (ECS) in the context of intrahepatic cholangiocarcinoma (iCCA). The search strategy was restricted to articles published in English and included clinical trials, randomized controlled trials, meta-analyses, systematic reviews, and observational studies. Studies involving animal models were excluded (see Table 6).

The initial search yielded 507 articles. Titles and abstracts were screened, and studies were excluded if they investigated cancer types other than iCCA or lacked relevance to lymph node pathology. The majority of articles concerning ECS pertained to head and neck malignancies. After applying the inclusion and exclusion criteria, five studies were deemed potentially relevant and were selected for abstract review (Appendix A, Table 7). Notably, none of these studies specifically addressed ECS in lymph node-positive iCCA.

2.2. Study design and setting

A retrospective, controlled cohort study was conducted to evaluate all patients who underwent surgical resection for intrahepatic cholangiocarcinoma (iCCA) at the University Medical Center Mainz, Germany, between January 1, 2008 and December 31, 2023. Inclusion criteria comprised patients who underwent curative-intent resection with histopathologically confirmed lymph node metastasis (N1 status). Patients were excluded if they displayed no nodal involvement (N0), had incomplete lymph node assessment (Nx), insufficient medical documentation, or histological evidence of a primary tumor of non-cholangiocarcinoma origin, such as hepatocellular carcinoma. The study cohort was divided into two groups based on the presence or absence of extracapsular tumor spread (ECS). The primary study group consisted of patients with confirmed ECS (N1/ECS+), defined as tumor extension beyond the lymph node capsule on histopathological examination. The control group comprised patients with nodal involvement in the absence of extracapsular spread (N1/ECS−).

The Primary endpoint was recurrence free survival, defined as interval (months) between surgery and first radiological evidence of disease recurrence or death from any cause. The secondary endpoint was overall survival (OS), defined as the duration (in months) from surgery to death from any cause. Patients were followed longitudinally through regular clinical assessments conducted either at our institution or by referring outpatient oncologists. Follow-up data were updated annually, and current survival and recurrence status were ascertained through direct contact with the patients' oncologists or family physicians.

2.3. Preoperative work up

The diagnosis was established using imaging modalities, including magnetic resonance imaging (MRI) or computed tomography (CT). Following diagnostic confirmation, each case was reviewed by a multidisciplinary tumor board. Surgical procedures were conducted by hepatopancreatobiliary (HPB)-experienced surgeons, with the decision to proceed based on the resectability of the tumor and the overall health status of the patient. For planned extended resections, preoperative volumetric analysis was performed to calculate the future liver remnant (FLR).

2.4. Postoperative pathological assessment

Histopathological examination of liver specimens and lymph nodes was performed by two experienced hepatopancreatobiliary (HPB) pathologists. Lymph node extracapsular tumor spread (ECS) was defined as either complete or focal disruption of the lymph node capsule with extension of tumor cells into the surrounding extranodal tissue. Cases in which no capsular infiltration was observed were classified as ECS-negative (ECS−). Routine reporting of ECS status was only recently introduced into the institutional pathology workflow. Consequently, archival pathology reports and preserved liver specimens from earlier years were systematically reviewed and re-evaluated by the HPB pathologists to determine ECS status. All specimens were available for reanalysis, as histological materials are archived for a minimum of 30 years in accordance with institutional policy.

All pathological assessments were conducted according to a standardized operating procedure (SOP), which ensured a consistent, reproducible, and reliable evaluation of histological parameters, including margin status and lymph node involvement.

2.5. Data recruitment and statistical analysis

All data was obtained from a prospective institutional database and analyzed using SPSS software (SPSS Inc., released 2014, IBM SPSS Statistics for Windows, Version 23.0, IBM, Armonk, NY, USA). The visualization of data was conducted using GraphPAD Prism (Version 10.3.1.). The analyzed variables included demographics (age, sex, BMI, comorbidities), surgical details (ASA score, type of resection), pathological findings (TNM classification, number of lymph nodes harvested, number of tumor-positive lymph nodes, R-stage, R1 margin site), and survival recurrence outcomes (date of death, date of recurrence, site of recurrence).

Data homogeneity between the two patient groups (N1/ECS+ and N1/ECS-) was assessed using the χ^2 test or Fisher's exact test for categorical variables and the Welch's *t*-test for continuous variables. Survival analysis was performed using the Kaplan-Meier method, with statistical significance evaluated by the log-rank test.

To minimize bias and account for potential confounders, a Cox regression analysis was conducted, adjusting for sex, resection type, clavien dindo >3a, tumor positive lymph nodes, R-stage, T-stage and ECS-stage. Additionally, a time-to-event analysis excluding patients with R1 resections, identified as potential confounders, was performed.

2.6. Ethical considerations

All enrolled patients provided informed consent, authorizing the collection of data and anonymous utilization for potential scientific analysis. In compliance with the stipulations outlined in the state hospital (§36 & §37) of the federal state, and in accordance with the directives of the independent ethics committee of Rhineland-Palatinate, no ethical approval was necessary for this study. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013).

3. Results

Between January 2008 and December 2023, a total of 344 patients underwent surgical resection for intrahepatic cholangiocarcinoma at the University Medical Center Mainz (Fig. 1). Of these, 273 patients were excluded from further analysis for the following reasons: locally advanced, unresectable disease (n = 80), absence of nodal involvement (N0) (n = 165), indeterminate nodal staging (Nx) (n = 26), or incomplete clinical records. Liver and lymph node specimens from the remaining 71 patients were re-evaluated by an expert hepatopancreatobiliary pathologist to confirm the presence or absence of extracapsular tumor spread. In one case, ECS status could not be conclusively determined due to insufficient tissue integrity.

Ultimately, 70 patients met the inclusion criteria and were included in the final statistical analysis. This cohort consisted of 30 patients with confirmed extracapsular tumor spread (N1/ECS+) and 40 patients with lymph noed involvement but without extracapsular spread (N1/ECS−). The median duration of follow-up was 14.4 months (range: 0–83 months).

3.1. Patients

In the N1/ECS + group, 30 % of patients were female (n = 9) and 70 % were male (n = 21), whereas in the N1/ECS- group, 55 % of patients were female (n = 22) and 45 % were male (n = 18) (p = 0.037). The median body mass index (BMI) was similar between the groups: 25.2 (SD ± 4.5) in the N1/ECS + group and 25.7 (SD ± 4.6) in the N1/ECS- group, with no significant difference observed (p = 0.835; CI 95 % −1.96-2.422).

Preoperative physical status was assessed using the American Society of Anesthesiologists (ASA) classification (Table 1). Although a lower proportion of patients in the ECS− group received adjuvant chemotherapy compared to the ECS + group, this difference did not reach statistical significance.

3.2. Operative details

Major hepatectomy was defined as resection including more than three liver segments. A total of 54 major hepatectomies (N1/ECS + n = 22; N1/ECS- n = 32) and 16 minor hepatectomies (N1/ECS + n = 8; N1/ECS- n = 8) were performed (p = 0.511). For a detailed describtion of surgical resections, refer to Table 2.

The overall median surgery time was 232 min (SD ± 115.9), with a median of 233 min (SD ± 86) in the N1/ECS + group and 227 min (SD ± 133) in the N1/ECS- group (p = 0.478). Lymph node dissection was meticulously performed in all surgeries.

3.3. Pathology work-up

The distribution of tumor stages was similar between the N1/ECS+

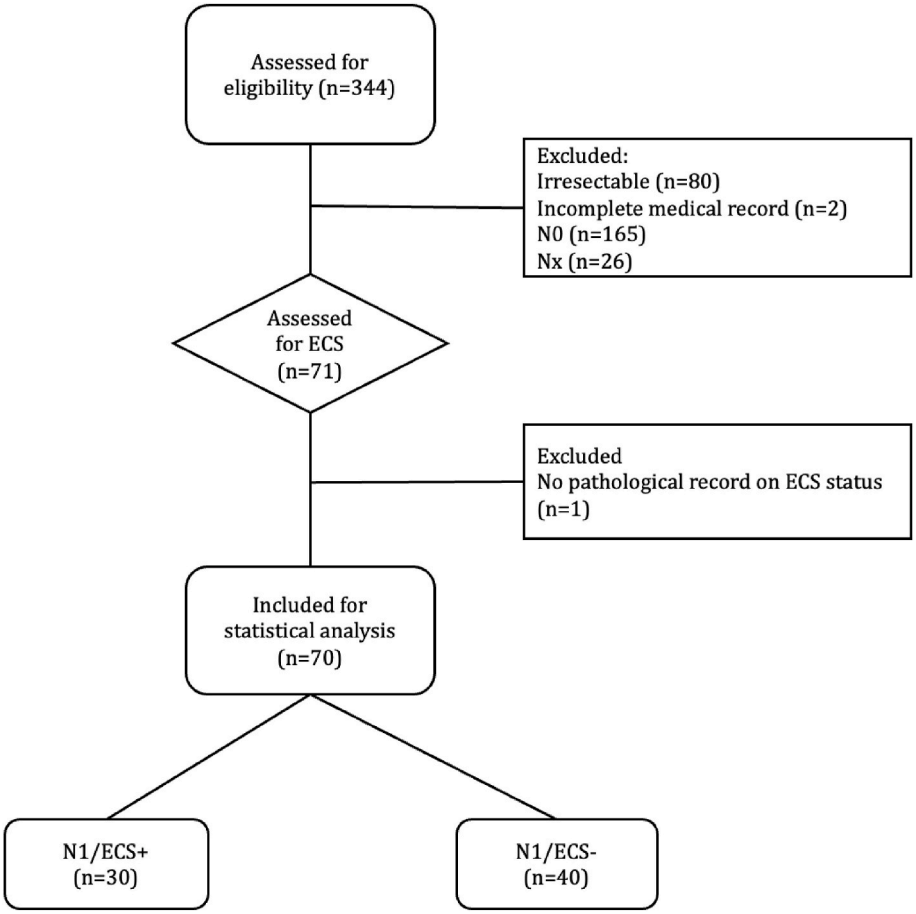

Fig. 1. Flowchart showing stepwise inclusion process.

Table 1
Categorical variables were tested for significance using the χ^2**test**, while continuous variables were analyzed using the Welch's *t*-test, which is robust to unequal variances. The results of the *t*-test are presented with 95 % confidence intervals (CI).

	N1/ECS + n = 30 (100 %)	N1/ECS– N = 40 (100 %)	p-value	CI 95 %	
				Upper border	Upper border
Total	30 (100 %)	40 (100 %)	–	–	–
Age – mean (SD)	61.0 (±11.7)	60.5 (10.3)	0.853	−5.89	4.89
Sex –					
Female	9 (30)	22 (55)	0.037	–	–
Male	21 (70)	18 (45)			
BMI -median (SD)	25.5 (±4.5)	25.3 (4.6)	0.835	−1.96	2.42
ASA					
I	0 (0)	1 (2.5)	0.412	–	–
II	12 (40)	21 (52.5)			
III	17 (56.7)	18 (45)			
Minor hepatectomy	8 (26.7)	8 (20)	0.511	–	–
Major hepatectomy	22 (73.3)	32 (80)			
Clavien Dindo >3a	12 (40)	17 (56.7)	0.834		
Comprehensive complication index mean	21.3 (9.9–32.7)	22.9 (14.0–31.8)	0.818	−12.55	15.83
TNM					
<T3	23 (76.7)	31 (77.5)	0.35	.	–
>T2	7 (23.3)	9 (22.5)	0.41	–	–
T1a	4 (13.3)	3 (7.5)			
T1b	7 (23.3)	8 (20)			
T2	12 (40)	20 (50)			
T3	0 (0)	5 (12.5)			
T4	7 (23.3)	4 (10)			
UICC/AJCC 8th Edition		36 (90)			
IIIB	25 (83.3)	4 (10)			
IV	5 (16.7)				
Lymph nodes examined -median (CI 95 %)	8 (5–9)	5(5–7)	0.785 0.052	−2.41- −2.44	3.181 0.014
Tumor positive lymph nodes median (CI95)	3 (2–5)	2 (2–3)			
R-Stage					
R0	22 (73.3)	31 (77.5)	0.687	–	–
R1	8 (26.7)	9 (22.5)			
Adjuvant chemotherapy	18 (60)	20 (50)	0.528	–	–

Table 2
Surgical resection type.

	N1/ECS + n = 30 (100 %)	N1/ECS – n = 40(100 %)
Right trisectionectomy	4 (13.3)	11 (27.5)
Left trisectionectomy	5 (16.7)	3 (7.5)
Right hepatectomy	5 (16.7)	5 (12.5)
Left hepatectomy	7 (23.3)	8 (20)
Resection of three liver segment	1 (3.3)	1 (2.5)
Bisegmentectomy	4 13.3)	5 (12.5)
Monosegmentectomy	2 (6.67)	0 (0)
Mesohepatectomy	0 (0)	5 (12.5)
Repeated resection	1 (3.3)	1 (2.5)

and N1/ECS− groups, with no statistically significant difference observed (p = 0.35; Table 1).

Positive resection margins (R1) were identified in 17 patients, including eight patients in the N1/ECS + group and nine patients in the N1/ECS- group. The primary site of R1 involvement was the parenchyma (N1/ECS + n = 7; N1/ECS- n = 7), followed by vascular margins (N1/ECS- n = 1) and bile duct margins (N1/ECS + n = 1; N1/ECS- n = 1).

The median number of lymph nodes harvested was five (SD ± 7) in the N1/ECS- group and eight (SD ± 4) in the N1/ECS + group (p = 0.785, 95 % CI: −2.415 to 3.181). The median number of tumor-positive lymph nodes was three (SD ± 3) in the N1/ECS + group and two (SD ± 2) in the N1/ECS- group, showing a trend toward statistically significant difference (p = 0.052, 95 % CI: −2.4 to 0.014).

3.4. Time to event analysis

The proportional hazards assumption was met for all Kaplan-Meier analyses. Fifty patients deceased during follow up (N1/ECS + n = 22 vs. N1/ECS- n = 28, p = 0.76). Median overall survival (OS) was equally distributed between the N1/ECS+ and N1/ECS- groups, with the N1/ECS + group showing a median OS of 17.3 months (95 % CI: 8.58–26.0) and the N1/ECS- group showing a median OS of 17.3 months (95 % CI: 9.96–24.69; p = 0.466) (Fig. 2). The 1-, 3-, and 5-year survival rates in the N1/ECS- group were 76 %, 20 %, and 8 %, respectively, compared to 58 %, 16 %, and 0 % in the N1/ECS + group.

Fifty patients experienced tumor recurrence after surgery (N1/ECS + n = 22 vs. N1/ECS- n = 28, p = 0.76). Median recurrence-free survival (RFS) did not differ significantly between the groups: 4.4 months (95 % CI: 1.34–7.47) in the N1/ECS + group versus 7.7 months (95 % CI: 6.01–9.37) in the N1/ECS- group (p = 0.335) (Fig. 3). The 1- and 3-year RFS rates in the N1/ECS + group were 27 % and 11 %, respectively, compared to 38 % and 7 % in the N1/ECS- group. The 5-year RFS rate was 7 % in the N1/ECS- group, while no patients in the N1/ECS + group survived recurrence-free for 5 years.

The sites of recurrence varied slightly between groups. In the N1/ECS + group, recurrence was hepatic in 23.3 % of cases (n = 7), extrahepatic in 20 % (n = 6), and both intra- and extrahepatic in 30 % (n = 9). No recurrence was observed in 26.7 % of patients (n = 8). In the N1/ECS- group, hepatic recurrence occurred in 25 % of cases (n = 10), extrahepatic in 22.5 % (n = 9), and both intra- and extrahepatic in 22.5 % (n = 9), while 30 % of patients (n = 12) experienced no recurrence.

A time-to-event analysis was performed with data adjusted to exclude patients with R1 resections. After adjustment, 31 patients

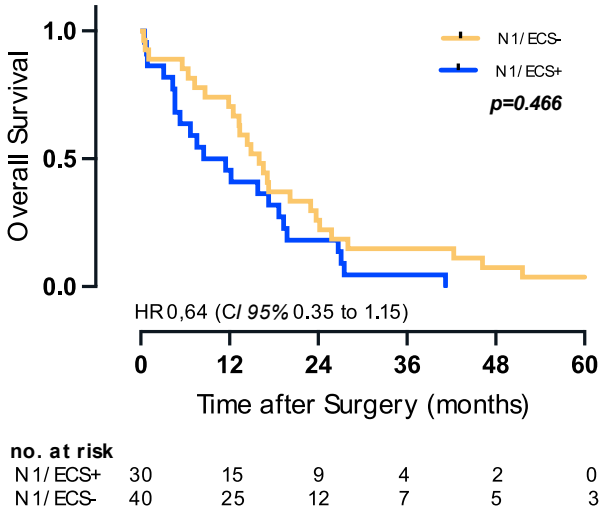

Fig. 2. Kaplan Meier curves presenting overall survival. median survival in the N1/ECS + group was 17.3 months and 17.3 in the N1/ECS- group, respectively. LogRank test revealed no statistically significant difference between both groups (p = 0.466).

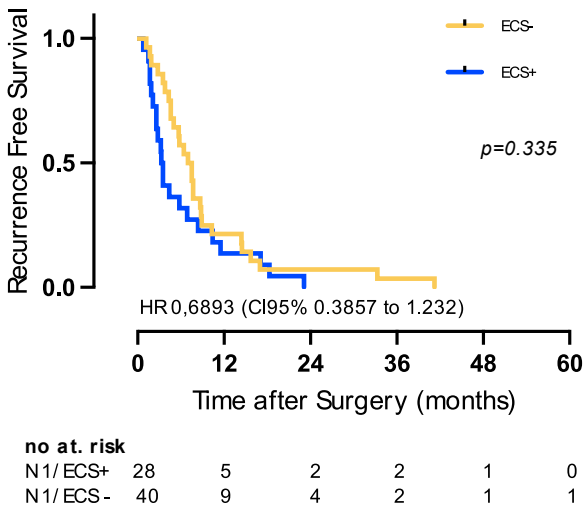

Fig. 3. Kaplan Meier curves presenting recurrence free survival (RFS). median RFS in the N1/ECS + group was 4.4 months and 7.7 in the N1/ECS- group, respectively. LogRank test revealed no statistically significant difference between both groups (p = 0.335).

remained in the N1/ECS- group and 22 in the N1/ECS + group. Adjusted median OS did not differ significantly between the groups: 18.7 months (95 % CI: 4.11–33.36) in the N1/ECS + group versus 20.2 months (95 % CI: 11.19–29.24) in the N1/ECS- group (p = 0.362). Adjusted 1-, 3-, and 5-year survival rates were 56 %, 14 %, and 0 % for the N1/ECS + group, compared to 79 %, 25 %, and 10 % for the N1/ECS- group.

After adjustment, the number of patients included in the recurrence-free survival (RFS) analysis was 20 in the N1/ECS + group and 31 in the N1/ECS- group. Adjusted median RFS did not differ significantly between the groups: 6.93 months (95 % CI: 1.41–12.47) in the N1/ECS + group versus 7.69 months (95 % CI: 5.74–9.65) in the N1/ECS- group (p = 0.481). The probability of RFS at 1, 3, and 5 years was 28 %, 9 %, and 0 % in the N1/ECS + group, compared to 39 %, 6 %, and 6 % in the N1/ECS- group, respectively.

A multivariable Cox proportional hazards regression analysis was performed to evaluate factors associated with overall survival (OS) and recurrence-free survival (RFS). The model included clinically relevant covariates: sex, type of surgical resection, Clavien–Dindo grade ≥ IIIa complication, number of tumor-positive lymph nodes, ECS status (N1/ECS + vs N1/ECS−), pathological T-stage, and resection margin status (R-stage). Sex was incorporated into the model due to the significant imbalance between groups, with a higher proportion of male patients in the ECS + cohort.

In the adjusted analysis for OS, only T2 stage was found to be significantly associated with decreased survival. In contrast, none of the included variables demonstrated a statistically significant association with RFS. Notably, ECS status did not independently influence either overall or recurrence-free survival in the multivariable model (Table 3, Table 4) (see Table 5).

4. Discussion

In this retrospective, single-center cohort study, we investigated the prognostic significance of extracapsular tumor spread (ECS) in patients undergoing liver resection for intrahepatic cholangiocarcinoma (iCCA) with confirmed lymph node involvement. To our knowledge, this is the first study to explore this association in the context of iCCA. A total of 70 N1 patients were included in the final analysis (N1/ECS + n = 30; N1/ECS− n = 40). Even after excluding patients with positive resection margins (R1) and adjusting time-to-event analyses for several clinically important variables ECS status was not found to be an independent predictor of recurrence-free survival (RFS) or overall survival (OS).Our findings indicate that the extension of tumor spread in lymph nodes might play a subordinate prognostic role in iCCA.

Although not statistically significant, a numerically shorter median RFS was observed in the ECS + group by 3.3 months (4.4 vs. 7.7 months). Nevertheless, this difference did not translate into a reduced overall survival, with median OS values nearly identical between groups (17.3 months in both cohorts).

In contrast to our findings, ECS is a known hallmark of aggressive tumor phenotype and appears to play an important role in various cancer entities [8]. For instance, Fujii et al. demonstrated in a small retrospective study of 46 patients with resected colon cancer that ECS+ was strongly associated with poorer recurrence-free survival (p < 0.01) [9].

There is broad consensus that lymph node metastases (LNM) play a central role in the progression and dissemination of iCCA [10,11]. Studies have shown, that lymph node invasion was associated with remarkably reduced survival, whereas tumor size alone has not been associated as independent prognostic marker [12]. The liver is the largest lymph producing organ, accounting for up to 50 % lymph and encompassing a highly intricate network of lymphatic channels [13,14]. Furthermore, recent evidence suggests a strong correlation between increased lymphatic tissue density and both tumor recurrence and lymph node metastasis in iCCA [15].

One plausible explanation for the absence of a distinct prognostic impact of extracapsular tumor spread in our cohort is the possibility that tumor cells disseminate through the lymphatic system at a rate that exceeds their capacity to breach the lymph node capsule. In other words, by the time ECS is histologically identifiable, metastatic dissemination may already be widespread. This rapid lymphatic spread may diminish the relative prognostic contribution of local extranodal extension, thereby masking any incremental effect of ECS on patient outcomes. In contrast to malignancies where ECS significantly impacts prognosis, iCCA is intrinsically associated with poor outcome [16]. The adverse impact of lymph node involvement in this disease is well documented, and may supersede any additional risk conferred by ECS. As

Table 3
Univariate and multivariate analysis of variables potentially influencing overall survival.

Variables	Kaplan-Meier (OS)	Multivariate Cox Regression (OS)		
	P	HR	CI	P
Sex – male (ref)	0.38	1.3	0.71–2.4	0.38
Resection (minor – ref)	0.42	0.97	0.43–2.17	0.95
CD (<3a<)	0.43	0.79	0.43–1.47	0.47
Tumor positive lymph nodes (<2<)	0.192	1.46	0.78–2.72	0.22
N1/ECS	0.466	1.30	0.73–2.3	0.36
T-stage (<2<)	0.031	1.98	1.02–3.85	0.04
R0	0.547	1.44	0.71–2.93	0.3

Table 4
Univariate and multivariate analysis of variables potentially influencing recurrence free survival.

Variables	Kaplan-Meier (OS)	Multivariate Cox Regression (OS)		
	P	HR	CI	P
Sex – male (ref)	0.43	1.3	0.7–2.4	0.4
Resection (minor – ref)	0.68	0.82	0.39–1.73	0.617
CD (<3a<)	0.11	0.5	0.26–0.95	0.034
Tumor positive lymph nodes (<2<)	0.12	1.65	0.9–3.0	0.48
N1/ECS-	0.67	1.23	0.67–2.25	0.48
T-stage (<2<)	0.17	1.58	0.82–3.0	0.17
R0	0.81	1.29	0.64–2.6	0.461

Table 5
1-year, 3-year and 5-year overall survival.

	1 YS	3 YS	5 YS
N1/ECS+	58 %	16 %	0
N1/ECS-	76 %	20 %	8 %

Table 6
1-year, 3-year and 5-year recurrence free survival.

	1 YS	3 YS	5 YS
N1/ECS+	27 %	11 %	0
N1/ECS-	38 %	7 %	7 %

demonstrated by Zhang et al., both the number of positive lymph nodes and the involvement of nodal stations beyond level 12 serve as strong indicators of poor prognosis [17]. These findings suggest that in the context of iCCA, ECS may exert only a marginal influence on survival.

Consistent with this interpretation, recurrence rates in our study were nearly identical between the N1/ECS+ and N1/ECS− groups (77.0 % vs. 73.3 %, respectively; $p = 0.76$). This observation further supports the hypothesis that ECS is not a reliable surrogate marker for a more aggressive tumor phenotype in iCCA.

The median number of lymph nodes harvested in our cohort was lower in the N1/ECS- group compared to the N1/ECS + group (N1/ECS-: $n = 5$ nodes vs. N1/ECS+: $n = 8$ nodes), with fewer tumor-positive lymph nodes observed in the N1/ECS + group (N1/ECS+: $n = 2$ nodes vs. N1/ECS-: $n = 3$ nodes, $p = 0.052$). The reduced lymph node yield in the ECS- group raises the possibility that cases of ECS + may have been underdiagnosed due to suboptimal nodal sampling. This potential limitation highlights the critical importance of meticulous lymphadenectomy and comprehensive pathological assessment in the surgical management of iCCA. Inadequate nodal evaluation may compromise staging accuracy and obscure meaningful prognostic markers such as ECS, thereby impeding appropriate risk stratification and therapeutic decision-making [15,16].

The role of lymphadenectomy in iCCA remains a subject of ongoing debate. Some authors have questioned its therapeutic value, arguing that it may increase the risk of additional morbidity without significantly improving survival outcomes [18,19]. In this context, we endorse the recommendations set forth in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, which advocate for the retrieval of a minimum of six lymph nodes. Particular emphasis is placed on harvesting nodes from portal stations 8 and 12, as delineated by the Japanese Society of Hepato-Biliary-Pancreatic Surgery [20,21]. This approach enhances the reliability of nodal staging and facilitates improved prognostic stratification and postoperative management.

Several authors demonstrated that lymph node involvement is one of the most significant predictors of poor long-term survival, with reported 5-year survival rates of ranging from 35 to 50 % for N0 patients compared to only 0–20 % for N1 patients [17,22].

Lymphadenectomy may improve precision of tumor staging, thereby allowing for a more accurate risk stratification and closer surveillance of patients with N1 disease. Although lymphadenectomy may not have a direct therapeutic effect, a significant proportion of iCCA patients experience recurrence in the hilar nodal basin. As suggested by Pawlik et al., lymphadenectomy may to help reduce the risk of locoregional recurrence in the hilar basin, potentially mitigating biliary obstruction and thereby contributing to improved quality of life [23].

In our institutional practice, extracapsular lymph node spread is routinely documented across a variety of gastrointestinal malignancies. Although this study did not demonstrate a statistically significant impact of ECS on overall survival in intrahepatic cholangiocarcinoma (iCCA), patients with N1/ECS + status exhibited a numerically shorter recurrence-free survival by 3.3 months compared to those without ECS.

While this difference did not reach statistical significance, it may represent a signal suggestive of prognostic relevance that could become apparent with a larger sample size. However, survival analyses beyond 36 months should be interpreted with caution, as the number of surviving patients becomes very small, rendering the Kaplan–Meier curves unstable and increasingly difficult to interpret.

Given the rarity of iCCA and the limited cohort available for this analysis, our findings underscore the need for further investigation. Future retrospective multicentre studies with expanded patient populations are warranted to validate our observations and explore the potential role of ECS as a prognostic marker. Only after such evidence has been established should a prospective trial be considered to more definitively assess the clinical significance of ECS in iCCA.

This study is limited by the retrospective design and the small sample size, which may have precluded the detection of a subtle but clinically relevant effect of extracapsular tumor spread on outcome. Rectifying this limitation is difficult due to the rarity of iCCA, which challenges the collection of larger patient cohorts and may lead to an underrepresentation of small yet significant effects. Another is the short follow up duration of median 14.4 months, however, since the prognosis in iCCA is generally poor, longer follow ups can be only achieved by improvent treatment procedures.

5. Conclusion

We performed as first a retrospective cohort study investigating the influence of extracapsular tumor spread in nodal positive (N1) patients with iCCA after curative resection. Tumorous infiltration of the lymph node capsula was not associated with reduced overall survival and recurrence free survival.

CRediT authorship contribution statement

Constantin Scholz: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. **Tiemo Sven Gerber:** Data curation, Resources. **Maria Hoppe-Lotichius:** Data curation. **Lisa Katherina Gröger:** Data curation. **Franziska Renger:** Data curation. **Monia Passalacqua:** Data curation. **Rabea Margies:** Data curation. **Beate Katharina Straub:** Data

Table 7
Studies included for abstract and text screening.

First author	Year	Study center	Study design	ECS	Objective
Rhee et al. (PMID 36689090)	2023	Yonsei University ollege of Medicine	RCT	No	Validating a scoring system to predict lymph node metastases prior to surgery based on imaging
Kambakamba et al. (PMID 26212390)	2015	University Hospital Zürich	Systematic review	No	Impact of lymph node count on prognostic staging
Ishii et al. (PMID 38580611)	2024	Graduate School of Medicine Kyoto	Meta-Analysis	no	Impact of lymph node dissection on overall survival
Amini et al. (PMID 25300798)	2014	John Hopkins Hospital Baltimore	Systematic review	No	Impact of lymph node dissection on overall survival
Gu et al. (PMID 270942524)	2016	Shanghai Jiao Tong University	Meta-Analysis	No	Prognostic significance of extended lymphadenectomy for biliary cancer with para-aortic lymph node metastases

curation, Resources. **Friedrich Foerster:** Data curation, Resources. **Arndt Weinmann:** Data curation, Resources. **Evangelos Tagkalos:** Methodology, Writing – review & editing. **Fabian Bartsch:** Conceptualization, Methodology, Software, Supervision, Validation, Writing – review & editing. **Hauke Lang:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of AI and AI-assisted technologies

After completion of the manuscript, the author(s) used ChatGPT 4.0. in order to improve readability in a few sentences and check for spelling mistakes.

Declaration of competing interest

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The remaining authors declare no conflict of interest.

Appendix A. search strategy for the literature review

(((((((cholangiocarcinoma)) OR (intrahepatic cholangiocarcinoma)) OR (biliary tract cancer)) OR (cholangiocelluar carcinoma)) AND (lymph node metastases)) OR (extracapsular lymph node spread)) OR (extracapsular tumor spread)) OR (extranodal extension)) OR (lymph node spread))

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