

ORIGINAL ARTICLE

Prognostic significance of lymph node ratio after resection of peri-hilar cholangiocarcinoma

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Abstract

Background: Lymph node (LN) metastases are a major negative prognostic factor for peri-hilar cholangiocarcinoma (PCC). Prognostic significance of the extent of LN dissection, number of metastatic LN and the lymph node ratio (LNR) are still under debate.

Aims: The aims of the present study were to evaluate the prognostic value of the LN status, the total number of LNs evaluated and LNR in PCC.

Methods: Between 1990 and 2008, 62 patients with PCC submitted to surgical resection with curative intent were retrospectively evaluated. Number and status of harvested LN were recorded.

Results: In 53 patients (85.4%) regional lymphadenectomy was performed. Median number of LNs examined was 7 (range 1–25). Median survival was 41.9 months in patients with N0 compared with 22.7 months in 21 patients (39.6%) with N+ ($P = 0.03$). Median survival was 3, 18.5 and 29 months for patients with 0, 1–3 and >3 LN retrieved, respectively ($P < 0.01$). Five-year survival for patients above and below the LNR cut-off value of 0.25 was 0% and 22.5%, respectively ($P = 0.03$).

Conclusions: LN metastases are a major prognostic factor for survival after surgical resection of PCC. The number of LN harvested and LNR showed high prognostic value.

Keywords

cholangiocarcinoma, surgery, prognostic factors

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Introduction

Cholangiocarcinoma is a rare but increasing worldwide tumour, originating from either intra- or extrahepatic bile.¹ Accordingly it is classified by its origin into intrahepatic (ICC), peri-hilar (PCC) or extrahepatic (EHC) cholangiocarcinoma.² Surgical treatment with radical intent is the only therapeutic option which has been shown to prolong survival.³ Several prognostic factors have been evaluated for cholangiocarcinoma. Among these, lymph node metastases is one of the most important prognostic factors. Several clinical studies described shorter survival in patients with positive lymph nodes, with a 5-year survival of 0–20%.^{4–8}

The extent of lymph node dissection and its prognostic value is still a matter of debate in the literature. Moreover the lymph node ratio (LNR) has been evaluated for different gastrointestinal tumours and has been shown to give greater prognostic stratification for patients with positive lymph nodes.^{9–11} Currently, within the literature there is only one study that evaluated LNR in cholangiocarcinoma.¹² This was limited to a cohort of patients with intrahepatic cholangiocarcinoma and hence no studies exist for peri-hilar cholangiocarcinoma.

The aims of the present study were to evaluate, in a cohort of patients submitted to surgical resection with curative intent for perihilar cholangiocarcinoma, the relationship between lymph nodes status and survival, the prognostic significance of the total number of resected lymph nodes and to evaluate the prognostic significance of the LNR.

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Methods

Retrospective analysis of sixty-two patients with PCC who underwent surgery with curative intent between 1990 and 2008 in a single Divisions of Surgery at University of Verona were included in the study. Written informed consent was obtained from each patient.

Pre-operative evaluation included blood chemistry tests with AST, ALT, ALP, GGT, direct and total bilirubin, blood count, PT, aPTT, albumin, CEA, CA19.9, alpha-fetoprotein and serology for hepatitis viruses (HBV and HCV). The tumour extension was evaluated with ultrasonography (US), colour Doppler ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). The differential diagnosis between cholangiocarcinoma and gastro-intestinal tumours liver metastases was made with tumour histology and by exclusion of other primary tumours using esophagogastroduodenoscopy and colonoscopy.

In patients with obstructive jaundice, the extension of the tumour was assessed using different diagnostic methods during the study period. Between 1990 and 1997, all of the patients underwent percutaneous *trans*-hepatic cholangiography (PTC) with the placement of single or multiple biliary drains; subsequently, mainly non-invasive diagnostic methods such as colangio-pancreatography MRI were used. All of the patients with obstructive jaundice (serum bilirubin level higher than 3 mg/dl) underwent percutaneous biliary drainage in order to define more precisely the longitudinal extension of the tumour and to resolve obstructive jaundice. In patients with segmental cholangitis multiple hepatic drainages of the excluded biliary segments were performed. More recently the use of CT-PET and diagnostic laparoscopy was introduced in selected patients.

During surgery, intra-operative US was routinely used in order to confirm pre-operative diagnosis, to evaluate the relationship between tumour and blood vessel and to evaluate the presence of intrahepatic metastases. The extent of liver resection was defined according to the Brisbane classification.¹³ Peri-operative death was defined as death within 30 days of the operation or at any point during the index hospitalization.

Lymphadenectomy of the regional lymph nodes was classified according to the classification of the Japanese Society of Biliary Surgery.¹⁴ Lymph nodes of the hepatoduodenal ligament (12h, 12a, 12p, 12b), the proper hepatic artery (8) and of the posterior surface of the head of the pancreas (13) were routinely dissected and retrieved; interaortocaval lymph nodes were retrieved when macroscopically abnormal. The surgical technique included complete dissection of the hilar structures, all the fatty and lymph node tissue surrounding the common hepatic artery, the main portal vein and the bile duct.

For the purposes of the present study, PCC was defined as tumours with involvement of structures of the hepatic hilus that often had required resection of the biliary confluence associated with liver and caudate lobe resection.^{7,15}

Microscopical invasion of the bile duct wall, the portal pedicle and the neural tissue was evaluated in each surgical specimen.

Vascular invasion was defined as neoplastic invasion of the arterial, portal or hepatic vessels confirmed by pathological examination.

After surgery patients were regularly followed up with blood tests, tumour markers (CEA and CA19.9) and an abdominal CT scan every 6 months.

From 2000 after surgery patients with lymph node metastases (N+) received adjuvant chemotherapy; adjuvant radiotherapy was reserved for patients with positive resection margins (R+).

Statistical analysis

The study data were prospectively collected and retrospectively analysed using SPSS statistical software (version 16.0; SPSS, Inc., Chicago, IL, USA). The hypothesis about the lack of an association between categorical variables was tested using Pearson's chi-squared test. Survival was modelled by means of a multivariate Cox's regression model. Factors that enter the model were selected using the univariate log-rank test. An association between selected factors and survival was graphically analysed using Kaplan–Meier curves. *P*-values < 0.05 were considered statistically significant.

Results

Sixty-two patients submitted to surgical resection for PCC with curative intent, from 1990 to 2008, were included in the present study. Clinical characteristics are summarized in Tables 1 and 2.

Radical resection (R0 resection) was obtained in 46 patients (76.7%). In 16 patients with positive margin resection (R1) tumor involved the proximal bile duct in 12, the distal bile duct in 2 and the liver parenchyma in 2.

Table 1 Patients characteristics

Variable (n = 62)	n (%)
Median age (range)	66 (30–84)
Median CA19.9 U/ml (range)	132 (9–6835)
Bile duct resection	62 (100)
Associated liver resection	54 (87)
Major hepatectomy	51 (82)
Caudate lobe resection	47 (76)
Portal vein resection/reconstruction	10 (16)
Hepatic artery resection/reconstruction	2 (3)
Regional lymph node dissection	53 (85)
Perineural invasion	50 (81)
Vascular invasion	35 (56)

Table 2 Type of surgical intervention in patients included in the study

Surgical procedure	N	%
Common bile duct resection	7	11.3
Common bile duct with caudate lobe resection	1	1.6
Bisegmentectomy	2	3.2
Bisegmentectomy with caudate lobe resection	1	1.6
Mesohepatectomy and caudate lobe resection (S1 + S4 + S5 + S8)	1	1.6
Left hepatectomy (S2 + S3 + S4)	4	6.5
Left hepatectomy and caudate lobe resection (S1 + S2 + S3 + S4)	23	37.1
Left trisectionectomy (S1 + S2 + S3 + S4 + S5 + S8)	2	3.2
Right hepatectomy (S5 + S6 + S7 + S8)	2	3.2
Right hepatectomy and caudate lobe resection (S1 + S5 + S6 + S7 + S8)	10	16.1
Right trisectionectomy and caudate lobe resection (S1 + S4 + S5 + S6 + S7 + S8)	9	14.6
Total	62	100.0

Table 3 Survival analysis for different subgroups of patients included into the study: number of patients, median survival with 95% confidence interval (CI), actuarial 3- and 5-year survival and *P*-value of the log rank test

Variable	<i>n</i>	Median survival (Months)	95% CI	3-y surv (%)	5-y surv (%)	<i>P</i>
Overall	62	21.9	18.2–25.5	30	15	–
LN						0.032
N0	32	41.9	13.3–70.4	50	25	
N+	21	22.7	18.2–27.2	0	0	
LN harvested						0.001
0 LN	9	3	1.0–5.9	0	0	
1–3 LN	18	18.5	12.7–24.2	25	16	
>3 LN	35	28.8	17.0–46.6	41	16	
Positive LN						0.721
1–3 N+	14	22.7	10.1–35.3	0	0	
>3 N+	7	25	–	0	0	
Negative LN						0.152
1–3 N0 examined	14	18.5	13.1–23.8	31	20	
>3 N0 examined	18	43.1	25.6–60.5	68	27	
LNR						0.031
≤0.25	42	26	16.2–35.8	44	22.5	
>0.25	9	22.7	1.0–45.0	0	0	

LN, lymph node; LNR, lymph node ratio.

Hospital mortality and morbidity were observed in 9.6% (6/62 patients) and 55% (34/62 patients), respectively; mortality was to 2/41 patients for time period 2000–08.

Regional lymphadenectomy was performed in 53 patients (85.4%), with a median number of harvested LN in this group of 7 (range 1–25).

LN metastases were present in 21 patients (39.6%). According to Japanese Society of Biliary Surgery¹⁴ classification LN metastases involved the N1 station in 21/53 patients (39.6%), the N2 station in 6/16 patients and the N3 station in 3/14.

Median follow-up for 56 (90.4%) patients who survived surgery was of 18.5 months (range 6–67 months).

Median survival was 21.9 months [95% confidence interval (CI) 18–26], with actuarial 3- and 5-year survival of 30% and 15%, respectively.

Survival analysis by LN status, number of LNs retrieved, number of positive LNs and LNR are shown in Table 3 and Figures 1–3.

Survival was not significantly different in patients with LN metastases in the N1, N2 and N3 stations with a median survival of 20, 22 and 25 months, respectively (*P* = 0.66).

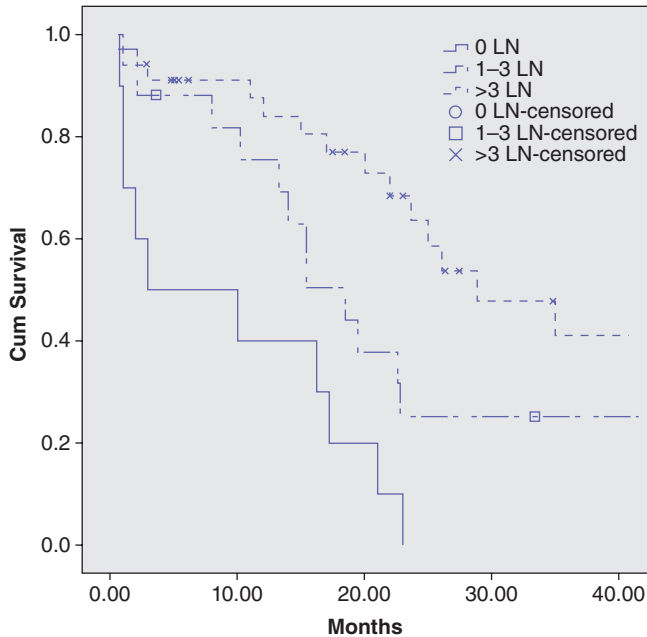


Figure 1 Survival curves in the subgroups by total number of harvested lymph nodes (LN). Survival was significantly related to the number of harvested LN (P -value of the log-rank test = 0.01)

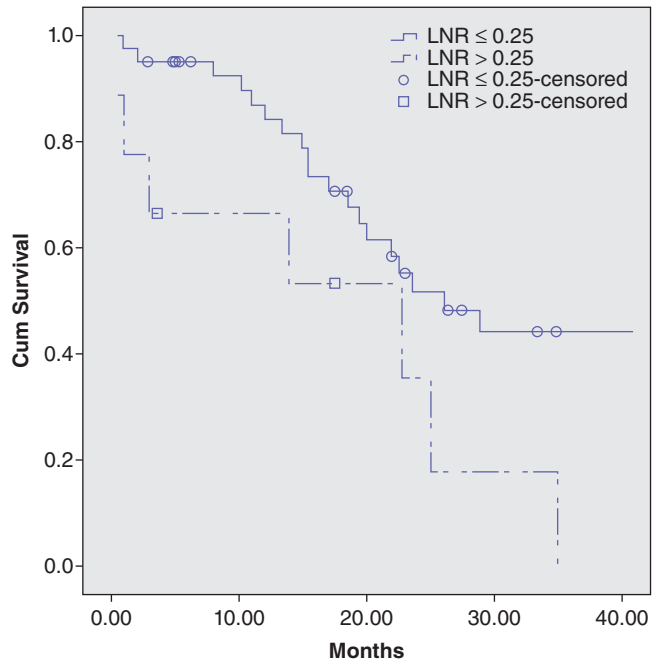


Figure 3 Survival curves in the subgroups by lymph node ratio (LNR). Survival was significantly longer in patients with LNR lower or equal to 0.25 ($P = 0.03$)

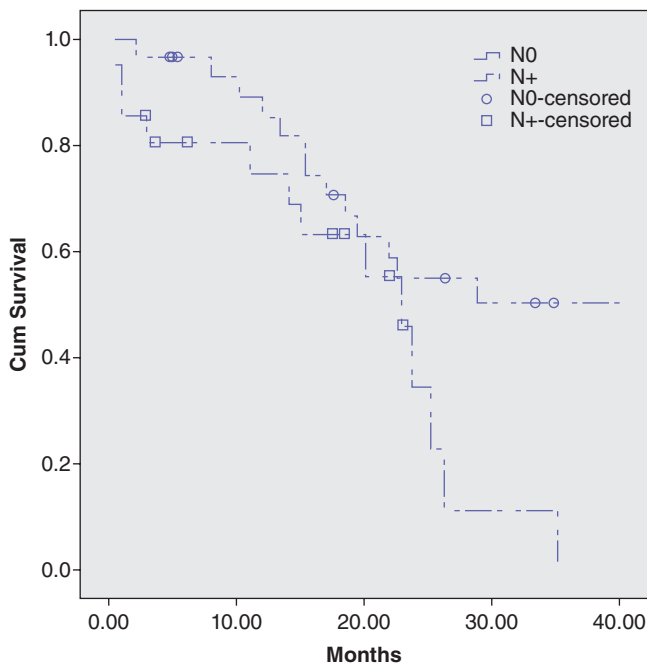


Figure 2 Survival curves in the subgroups by lymph node (LN) status. Survival was significantly shorter in N+ patients ($P = 0.03$)

In the group with no LN metastases patients with 1–3 LN harvested showed a median survival of 18.5 compared with 43.1 months for patients with more than 3 LN examined, the difference did not reach statistical significance ($P = 0.152$) (Table 3).

Table 4 Multivariate survival analysis using Cox’s proportional hazards model: estimated hazard ratios, 95% confidence interval (CI) and P -values of the hypothesis test about independence between factors and survival

Variable	HR	95% CI	P
LNR >0.25 vs. ≤0.25	3.16	1.16–8.62	0.024
R1 vs. R0	4.40	1.19–16.24	0.026
TNM stage	1.52	0.78–3.01	0.229
Macroscopic vascular invasion	0.83	0.27–2.47	0.741
Perineural invasion	0.31	0.79–1.27	0.105

LNR, lymph node ratio.

In order to evaluate the prognostic significance of LN metastases and its relationship with the total number of LN harvested, we evaluated the LNR with a cut-off value of 0.25.

Multivariate survival analysis using Cox’s proportional hazards model (Table 4) showed that factors significantly related with survival were surgical radicality and LNR with hazard ratios of 4.40 (95% CI 1.19–16.24) and 3.16 (1.16–8.62), respectively.

Discussion

LN metastases are a major prognostic factor in the treatment of perihilar cholangiocarcinoma; 30–50% of patients who undergo surgical resection will have nodal involvement.^{2,16–19}

Within the literature 5-year survival for positive node patients does not reach 20%,^{4–8} and similar findings have been shown in

the present study. The prevalence of non-regional lymphnode metastases, defined as M1 according to the UICC TNM, is not well known in hilar cholangiocarcinoma as systematic dissection of non-regional lymphnodes is not routinely performed in the majority of centres. Kitagawa *et al.* identified a prevalence of positive para-aortic lymph nodes of 17% and reported a 5-year survival of 14% in this group of patients.¹⁷ Moreover, 5-year survival decreased to 0% in patients with macroscopically and microscopically positive para-aortic lymph nodes.¹⁷

The extent of LN dissection is still a matter of debate in literature. According to 7th edn the *AJCC/UICC Guidelines* at least three LN should be harvested for adequate staging of perihilar cholangiocarcinoma.²⁰ In a recent study, Ito *et al.* demonstrated the relationship between the total number of LN examined and survival in patients without LN metastases.²¹ Ito *et al.* identified an optimum cut-off value for hilar cholangiocarcinoma of seven LN for a higher disease-specific survival for N0 patients.²¹ In the current study the median number of examined lymphnodes was greater than 7, a result that is similar to other data in literature.¹²

The multi-institutional US study based upon the Surveillance, Epidemiology and End Results (SEER) database identified a significant relationship between the number of examined lymphnodes in N0 patients submitted for surgical resection for extrahepatic bile duct cancer, gallbladder cancer or ampullary carcinoma.²² The authors reported a median survival of 21 and 34 months for patients with 1 to 2 and more than 10 lymph nodes examined, respectively.²² Moreover, the authors identified a relationship between the number of positive LN and survival.²² However, the major limitation of this study was that the authors included different types of tumours with known different biological behaviour.²²

This issue had not been clearly demonstrated in patient with peri-hilar cholangiocarcinoma.

In the present study the value of systematic regional lymphadenectomy has been confirmed. Patients with more than three LN harvested showed longer survival. Within the literature no data are available regarding the therapeutic value of lymphadenectomy in the bile duct and liver cancers but a systematic dissection of regional LN improves staging of the disease, stratification of patients and could increase survival in selected groups of patients.

In order to investigate the prognostic value of the number of positive LN and its relationship with the total number of LN harvested the present study also evaluated the LNR.

LNR has demonstrated its prognostic value in oesophageal, gastric, colorectal and pancreatic cancer.^{9–11} Recently the prognostic value of LNR was also demonstrated in intrahepatic cholangiocarcinoma.¹² To the authors knowledge no studies have analysed this issue in perihilar cholangiocarcinoma. The present study has identified a relationship between survival and LNR demonstrating the prognostic value of this factor. Moreover in our sample a cut-off value of 0.25 demonstrated its prognostic value in univariate and multivariate analysis. The LNR can be applied in clinical practice to stratify more accurately patients after surgical resec-

tion. The current analysis also demonstrated that patients with LN metastases can have long-term survival if LNR is below 0.25.

Conclusions

LN metastases is a major prognostic factors for survival after surgical resection of PCC. The number of LN harvested and LNR showed a prognostic value. Likewise of other gastrointestinal tumours, the present study identifies the prognostic role of LNR also in PCC.

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