

## Retrospective Study

# Correlation between metastatic lymph node ratio and prognosis in patients with extrahepatic cholangiocarcinoma

Jian-Wei Zhang, Yun-Mian Chu, Zhong-Min Lan, Xiao-Long Tang, Ying-Tai Chen, Cheng-Feng Wang, Xu Che

Jian-Wei Zhang, Yun-Mian Chu, Zhong-Min Lan, Xiao-Long Tang, Ying-Tai Chen, Cheng-Feng Wang, Xu Che, Department of Abdominal Surgery, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

**Author contributions:** Zhang JW and Chu YM contributed equally to this work; Che X designed the research; Chu YM, Lan ZM and Tang XL performed the research; Zhang JW contributed new reagents/analytic tools; Chen YT and Wang CF analyzed the data; Chu YM and Lan ZM wrote the paper.

**Ethics approval:** The study was reviewed and approved by the Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Institutional Review Board.

**Informed consent:** All study participants or their legal guardian provided informed written consent prior to study enrollment.

**Data sharing:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Xu Che, MD, Department of Abdominal Surgery, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. [xu.che@cicams.ac.cn](mailto:xu.che@cicams.ac.cn)  
Telephone: +86-10-87787120

Fax: +86-10-87787120

Received: September 30, 2014

Peer-review started: October 14, 2014

First decision: October 29, 2014

Revised: January 16, 2015

Accepted: February 11, 2015

Article in press: February 11, 2015

Published online: April 14, 2015

lymph node ratio (MLNR) in extrahepatic cholangiocarcinoma (ECC) patients undergoing radical resection.

**METHODS:** Seventy-eight patients with ECC were enrolled. Associations between various clinicopathologic factors and prognosis were investigated by Kaplan-Meier analyses. The Cox proportional-hazards model was used for multivariate survival analysis.

**RESULTS:** The overall three- and five-year survival rates were 47.26% and 23.99%, respectively. MLNR of 0, 0-0.2, 0.2-0.5, and > 0.5 corresponded to five-year survival rates of 28.59%, 21.60%, 18.84%, and 10.03%, respectively. Univariate analysis showed that degree of tumor differentiation, lymph node metastasis, MLNR, tumor-node-metastasis (TNM) stage, and margin status were closely associated with postoperative survival in ECC patients ( $P < 0.05$ ). Multivariate analysis showed that MLNR and TNM stage were independent prognostic factors after pancreaticoduodenectomy (HR = 2.13, 95%CI: 1.45-3.11;  $P < 0.01$ ; and HR = 1.97, 95%CI: 1.17-3.31;  $P = 0.01$ , respectively). The median survival time for MLNR > 0.5, 0.2-0.5, 0-0.2, and 0 was 15 mo, 24 mo, 23 mo, and 35.5 mo, respectively. There were statistical differences in survival time between patients with different MLNR ( $\chi^2 = 15.38$ ;  $P < 0.01$ ).

**CONCLUSION:** MLNR is an independent prognostic factor for ECC patients after radical resection and is useful for predicting postoperative survival.

**Key words:** Cholangiocarcinoma; Metastatic lymph node; Prognosis; Surgery

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This study aims to investigate the prognostic significance of metastatic lymph node ratio in extrahepatic cholangiocarcinoma patients undergoing radical resection. Using univariate and multivariate

## Abstract

**AIM:** To investigate the prognostic value of metastatic

analysis, we found that metastatic lymph node ratio was an independent prognostic factor for these patients after radical resection and is useful for predicting postoperative survival.

Zhang JW, Chu YM, Lan ZM, Tang XL, Chen YT, Wang CF, Che X. Correlation between metastatic lymph node ratio and prognosis in patients with extrahepatic cholangiocarcinoma. *World J Gastroenterol* 2015; 21(14): 4255-4260 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i14/4255.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i14.4255>

## INTRODUCTION

Cholangiocarcinoma (CCA) is a malignant tumor that originates from the intra- and extrahepatic biliary epithelium, and it accounts for approximately 3% of all gastrointestinal malignancies<sup>[1]</sup>. Patients with liver fluke infestation, chronic viral hepatitis, choledochal cysts, and primary sclerosing cholangitis can develop CCA<sup>[2]</sup>. Intrahepatic CCA arises within the hepatic parenchyma, and most often presents as a mass lesion without major bile duct obstruction or jaundice<sup>[3]</sup>. Extrahepatic cholangiocarcinoma (ECC) is defined as common bile duct CCA, which accounts for 20%-40% of CCA cases<sup>[4]</sup>. At present, surgical resection remains the only treatment choice for ECC patients. However, the curative rate of ECC has been low for patients in advanced stages<sup>[5]</sup>. Even with complete resection of the tumors, most patients are subject to local recurrence or distant metastasis<sup>[6]</sup>. According to the staging of extrahepatic bile duct cancer, the number of metastatic lymph nodes is a key parameter for tumor staging and prognosis prediction. Lymph node metastasis is a prognostic factor for survival of ECC patients after curative resection<sup>[7]</sup>, and those with peripheral lymph node metastases had notably poorer prognosis.

Metastatic lymph node ratio (MLNR), the ratio of the number of metastatic lymph nodes to the number of lymph nodes removed, is regarded as an important prognostic factor for various tumors<sup>[8-14]</sup>. However, there are few studies examining the association between MLNR and prognosis in ECC patients. In this study, we analyzed multiple clinicopathologic factors in ECC patients, and investigated the potential association between lymph node metastasis and prognosis. We aimed to find reliable indicators for predicting the prognosis of ECC patients following radical resection.

## MATERIALS AND METHODS

### Study population

A total of 128 ECC patients were recruited from the Cancer Hospital of Chinese Academy of Medical Sciences between January 1999 and January 2012.

The recruited patients needed to meet the following inclusion criteria: (1) complete clinical data available; (2) pathologically confirmed ECC after surgery; (3) neoadjuvant chemoradiotherapy-naïve before surgery; (4) complete follow-up record available (until January 2014); and (5) absence of liver disease or other diseases. All patients received pancreaticoduodenectomy and preoperative assessment, including a detailed history and physical, laboratory, and radiologic examinations. All patients underwent enhanced abdominal CT/magnetic resonance imaging, abdominal ultrasound, and determination of serum tumor markers.

The tumors were classified based on the tumor-node-metastasis (TNM) classification criteria of the American Joint Committee on Cancer (AJCC), 6<sup>th</sup> edition<sup>[15]</sup>. The clinicopathologic data analyzed in this study included: age, sex, duration of operation, intra-operative blood loss, tumor differentiation, tumor embolism, perineural invasion, T component of TNM stage, TNM stage, margin status, postoperative adjuvant chemotherapy, total number of dissected lymph nodes, lymph node status, and MLNR.

All patients underwent lymphadenectomy; based on the Japanese Pancreatic Society classification of pancreatic cancer, the extent of lymphadenectomy was defined as follows: around the pancreas and duodenum (stations 13 and 17), inside the hepatoduodenal ligament (station 12), around the stomach (stations 1-6), around the hepatic artery proper (station 8), and around the superior mesenteric artery (station 14).

Data on the total number of lymph nodes dissected and the number of lymph node metastases were obtained from pathologic reports. Patients were divided into four groups according to the MLNR values: patients with negative lymph nodes (MLNR = 0), and patients with positive lymph nodes (0 < MLNR < 0.2, 0.2 < MLNR < 0.5 and 0.5 < MLNR).

### Follow-up

Follow-up was performed *via* telephone or mail, and all outpatient records were reviewed. The first follow-up visit was made at 6 mo after surgery. It was then continued every 6-12 mo until March 2014.

### Statistical analysis

Statistical analysis was performed using the SAS v 9.2 (SAS Institute Inc., Cary, NC, United States). The life-table method was used to calculate the three- and five-year survivals. The Kaplan-Meier method was used to construct survival curves, which were compared using the log-rank test. Multivariate analysis of prognostic factors was performed using the Cox proportional-hazards model. Survival was calculated from the day of surgery to the time of death (for non-surviving patients) or to the last follow-up (until March 2014 for surviving patients or patients who dropped out). *P* < 0.05 was considered statistically significant.

**Table 1 Clinicopathologic factors and prognosis**

Clinicopathologic factors	No. of patients	Survival (%)		<i>P</i> value <sup>a</sup>
		3-yr	5-yr	
Total cases	78	47.26	23.99	0.388
Age (yr)				
≤ 60	46	57.14	28.57	
> 60	32	45.22	26.65	0.748
Sex				
Male	51	46.92	21.90	
Female	27	48.48	36.36	0.763
Duration of surgery (min)				
≤ 300	41	46.27	27.76	
> 300	37	47.98	18.66	0.337
Intraoperative blood loss (mL)				
≤ 500	47	57.14	28.57	
> 500	31	46.34	26.42	< 0.01
Differentiation degree				
Highly	24	61.32	33.45	
Moderately	44	50.00	28.04	0.435
Poorly	10	23.08	15.38	
Perineural invasion				
Yes	57	38.72	14.75	0.183
No	21	68.38	48.84	
Tumor embolism				
Yes	3	33.33	33.33	0.369
No	75	47.94	25.68	
T stage				
T1	2	100	50	0.179
T2	7	53.07	33.77	
T3	24	46.05	21.98	
T4	45	37.40	18.70	0.010
Total number of lymph node dissected				
≤ 15	30	45.92	26.53	
> 15	48	39.39	26.26	0.002
Lymph node metastasis				
Yes	55	37.74	17.56	
No	23	70.13	28.59	0.044
MLNR				
0	23	70.13	28.59	
0-0.2	12	54.01	21.60	0.043
0.2-0.5	18	48.34	18.84	
> 0.5	25	33.67	10.03	
TNM stage				0.055
I	2	54.83	27.95	
II	26	41.67	21.03	
III	50	35.06	17.53	0.043
Cutting edge				
Negative	75	54.36	25.02	
Positive	3	33.33	10.00	0.055
Postoperative chemotherapy				
Yes	64	54.55	22.02	
No	14	46.80	22.40	

<sup>a</sup>Log-rank test. MLNR: Metastatic lymph node ratio; TNM: Tumor-node-metastasis.

## RESULTS

### Patient general data

Seventy-eight patients, including 51 men and 27 women, were included in the final analysis. Their average age was 60.2 years, ranging from 42 to 78 years. Two patients were classified as stage I, 26 as stage II, and 50 as stage III. Fifty-five patients were diagnosed with lymph node metastasis. The average number of dissected lymph nodes was 15.4 (range:

**Table 2 Multivariate analysis for predictive factors of extrahepatic cholangiocarcinoma patient survival**

Factors	$\beta$	SD	$\chi^2$	<i>P</i> value	HR	95%CI
MLNR	0.75	0.19	15.01	< 0.01	2.13	1.45-3.11
TNM stage	0.67	0.26	6.55	0.011	1.97	1.17-3.31

MLNR: Metastatic lymph node ratio; TNM: Tumor-node-metastasis.

10-36). Forty-two patients were lost to follow-up. Eight patients were excluded, among who four were without complete clinical information, two were diagnosed with non-ECC, one had received adjuvant chemotherapy before operation, and one had received interventional chemotherapy before operation.

### Survival rates

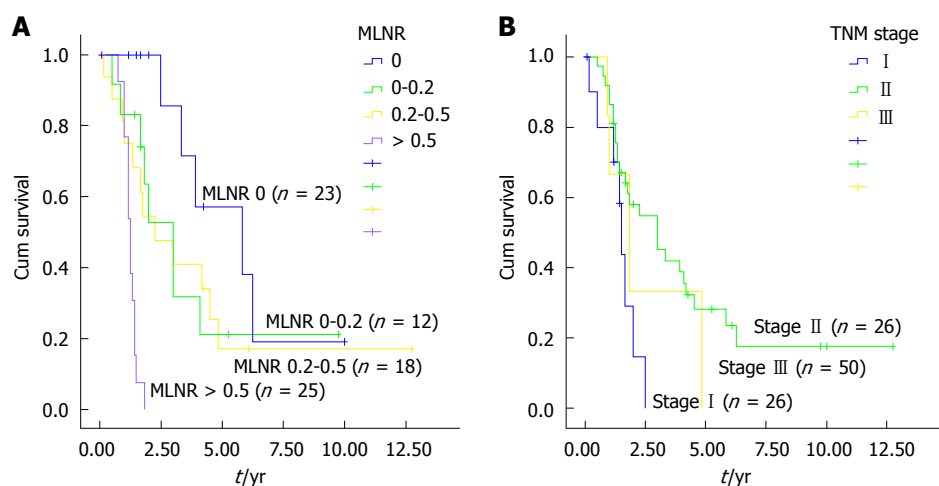
The overall three- and five-year survival rates were 47.26% and 23.99%, respectively. There were no statistically significant differences in the survival rates with regard to age, sex, duration of surgery, intraoperative blood loss, perineural invasion, tumor embolism, T stage, number of lymph node dissected, or postoperative chemotherapy. The three- and five-year survival rates of patients with peripheral lymph node metastasis (37.74% and 17.56%, respectively) were lower than those without peripheral lymph node metastasis (70.13% and 28.59%, respectively), and the differences were statistically significant ( $P$ s < 0.05). Five-year survival rates according to MLNR were: 28.59% (MLNR = 0), 21.60% (MLNR = 0-0.2), 18.84% (MLNR = 0.2-0.5), and 10.03% (MLNR > 0.05).

### Associations between clinicopathologic factors and postoperative survival

Univariate analyses showed that degree of tumor differentiation, lymph node metastasis, MLNR, TNM stage, and margin status were significantly correlated with postoperative survival in ECC patients (all  $P$  < 0.05) (Table 1). Furthermore, the Cox proportional-hazard model for multivariate analysis was used to further investigate these factors, showing that MLNR and TNM stage were independent predictors of survival (Table 2).

### Survival curves

To further determine the effects of MLNR and TNM stage on prognosis of patients, survival curves were established. Median survival time for regional lymph node metastases > 0.5, 0.2-0.5, 0-0.2, and 0 were 15 mo, 24 mo, 23 mo, and 35.5 mo, respectively. The log-rank test revealed significant differences in survival time among patients with different MLNR values ( $\chi^2$  = 15.376;  $P$  < 0.01) (Figure 1A). Median survival time for TNM stage I, II, and III were 15.5 mo, 24.0 mo, 23.0 mo, and 35.5 mo, respectively, with significant differences ( $\chi^2$  = 15.376;  $P$  < 0.01) (Figure 1B).



**Figure 1** Survival curves of extrahepatic cholangiocarcinoma patients using a Cox model. A: Survival curves of extrahepatic cholangiocarcinoma (ECC) patients with different metastatic lymph node ratio (MLNR) values; B: Survival curves of ECC patients with different tumor-node-metastasis (TNM) stages.

## DISCUSSION

Some factors have been found for the prognosis of CCA<sup>[16-21]</sup>. However, there are few studies on survival outcomes and prognostic factors of ECC patients<sup>[22]</sup>. The TNM staging system has been widely applied as a simple, convenient, and repeatable method. For ECC patients, the N component, or description of the involvement of regional lymph nodes, is based on the number and location of metastatic lymph nodes retrieved intraoperatively, and is used to predict prognosis. According to the 6<sup>th</sup> edition of the AJCC Cancer Staging Manual, lymphadenectomy should be considered in patients with more than 15 lymph nodes, which is evaluated as the N component of the TNM stage<sup>[23]</sup>. All these indicate that the N component may not accurately predict prognosis of ECC patients with fewer than 15 lymph nodes removed. However, the number of lymph nodes removed is often dictated by the knowledge and skill of the surgeon and pathologist. Therefore, MLNR is a more reliable prognostic factor than the number of metastatic lymph nodes<sup>[24]</sup>, and the prognostic value of MLNR is not influenced by the scope of lymph node dissection<sup>[25-27]</sup>.

In the present study, we performed univariate and multivariate analyses to investigate the role of MLNR in prognosis prediction of ECC patients, and found that MLNR is an independent prognostic factor. We also analyzed the prognostic values of other lymph node-related indicators and found that lymph node metastasis, but not the total number of lymph nodes dissected, was closely associated with prognosis. In a retrospective analysis of 93 intrahepatic CCA patients, Tamandl *et al.*<sup>[28]</sup> verified that the total number of lymph nodes dissected was not associated with prognosis. Although no evidence has demonstrated that dissection of more lymph nodes improves the prognosis, extended lymphadenectomy can more accurately identify the status of lymph node metastasis and predict prognosis<sup>[29]</sup>. As the scope of lymphadenectomy during

radical resection of ECC remains controversial, MLNR is particularly important for evaluating the prognosis of ECC patients, which can represent the number and location of metastatic lymph nodes. Furthermore, calculation of MLNR is a simple and highly repeatable method for stratification of outcomes and takes into account not only the number of dissected lymph nodes, but also biologic behavior (*i.e.*, number of positive lymph nodes).

In the present study, MLNR was found to be an independent prognostic indicator of long-term patient survival; a higher MLNR value predicted poorer biologic behavior and prognosis. MLNR can be used in postoperative stratification of ECC patients, *i.e.*, assessment of the appropriateness of further treatment or enrollment in future clinical trials.

In summary, MLNR is an independent prognostic factor for ECC patients who underwent pancreaticoduodenal resection. MLNR can be used as an important tool in postoperative pathologic evaluation to predict prognosis and facilitate stratification for treatment. More cases of ECC should be considered in further studies for verifying the association between MLNR and survival.

## COMMENTS

### Background

Extrahepatic cholangiocarcinoma (ECC) is a gastrointestinal malignancy with poor prognosis. Surgical resection remains the only treatment choice for ECC. However, the curative rate of ECC has been low for patients diagnosed with advanced stages. There are no effective methods for predicting postoperative survival of patients with ECC.

### Research frontiers

Metastatic lymph node ratio (MLNR), the ratio of the number of metastatic lymph nodes to the number of lymph nodes removed, is known as an important prognostic factor for various tumors.

### Innovations and breakthroughs

There are few studies examining the association between MLNR and prognosis in ECC patients. The authors firstly investigated the prognostic factors for ECC in a Chinese population. A total of 128 ECC cases were collected from January



1999 to January 2012. Multivariate analysis was performed to investigate the association between clinicopathologic factors and the survival of ECC patients. The Kaplan-Meier method was used to construct survival curves and to investigate the clinicopathologic factors for the survival of ECC patients.

### Applications

MLNR is an independent prognostic factor for patients with ECC after radical resection, which may be used as an index for predicting postoperative survival.

### Terminology

Cholangiocarcinoma is a malignant tumor that originates from the intra- and extrahepatic biliary epithelium, and accounts for ~3% of all gastrointestinal malignancies. ECC is defined as cholangiocarcinoma of the common bile duct, which accounts for 20-40% of the cases.

### Peer-review

It is a good retrospective study in which the authors investigated the prognostic factors for patients with ECC. The results are interesting and suggest that MLNR is an independent prognostic factor for patients with distal cholangiocarcinoma after radical resection and is useful for predicting postoperative survival.

## REFERENCES

- Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang YY, Wangnon S, Sripa B, Hong ST. Epidemiology of cholangiocarcinoma: an update focusing on risk factors. *Cancer Sci* 2010; **101**: 579-585 [PMID: 20085587 DOI: 10.1111/j.1349-7006.2009.01458.x]
- Braconi C, Patel T. Cholangiocarcinoma: new insights into disease pathogenesis and biology. *Infect Dis Clin North Am* 2010; **24**: 871-84, vii [PMID: 20937455 DOI: 10.1016/j.idc.2010.07.006]
- Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; **60**: 1268-1289 [PMID: 24681130 DOI: 10.1016/j.jhep.2014.01.021]
- Nishimura M, Naka S, Hanazawa K, Tani T, Fukami M, Okada S, Fujiyama Y. Cholangiocarcinoma in the distal bile duct: a probable etiologic association with choledocholithiasis. *Dig Dis Sci* 2005; **50**: 2153-2158 [PMID: 16240231 DOI: 10.1007/s10620-005-3023-9]
- Gwak HK, Kim WC, Kim HJ, Park JH. Extrahepatic bile duct cancers: surgery alone versus surgery plus postoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 2010; **78**: 194-198 [PMID: 19910130 DOI: 10.1016/j.ijrobp.2009.07.003]
- Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakamura H, Nakashima A, Sueda T. Adjuvant gemcitabine plus S-1 chemotherapy improves survival after aggressive surgical resection for advanced biliary carcinoma. *Ann Surg* 2009; **250**: 950-956 [PMID: 19953713 DOI: 10.1097/SLA.0b013e3181bf0c8b]
- Kim HJ, Kim CY, Hur YH, Koh YS, Kim JC, Kim HJ, Cho CK. The prognostic factors for survival after curative resection of distal cholangiocarcinoma: perineural invasion and lymphovascular invasion. *Surg Today* 2014; **44**: 1879-1886 [PMID: 24535697 DOI: 10.1007/s00595-014-0846-z]
- Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 2005; **23**: 8706-8712 [PMID: 16314630 DOI: 10.1200/JCO.2005.02.8852]
- Nitti D, Marchet A, Olivieri M, Ambrosi A, Mencarelli R, Belluco C, Lise M. Ratio between metastatic and examined lymph nodes is an independent prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. *Ann Surg Oncol* 2003; **10**: 1077-1085 [PMID: 14597447 DOI: 10.1245/ASO.2003.03.520]
- Riediger H, Keck T, Wellner U, zur Hausen A, Adam U, Hopt UT, Makowiec F. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg* 2009; **13**: 1337-1344 [PMID: 19418101 DOI: 10.1007/s11605-009-0919-2]
- Vinh-Hung V, Verkooyen HM, Fioretta G, Neyroud-Caspar I, Rapiti E, Vlastos G, Deglise C, Usel M, Lutz JM, Bouchardy C. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. *J Clin Oncol* 2009; **27**: 1062-1068 [PMID: 19164210 DOI: 10.1200/JCO.2008.18.6965]
- Liu YP, Ma L, Wang SJ, Chen YN, Wu GX, Han M, Wang XL. Prognostic value of lymph node metastases and lymph node ratio in esophageal squamous cell carcinoma. *Eur J Surg Oncol* 2010; **36**: 155-159 [PMID: 19854606 DOI: 10.1016/j.ejso.2009.09.005]
- Falconi M, Crippa S, Domínguez I, Barugola G, Capelli P, Marcucci S, Beghelli S, Scarpa A, Bassi C, Pederzoli P. Prognostic relevance of lymph node ratio and number of resected nodes after curative resection of ampulla of Vater carcinoma. *Ann Surg Oncol* 2008; **15**: 3178-3186 [PMID: 18712568 DOI: 10.1245/s10434-008-0099-4]
- Espín F, Bianchi A, Llorca S, Feliu J, Palomera E, García O, Remon J, Suñol X. Metastatic lymph node ratio versus number of metastatic lymph nodes as a prognostic factor in gastric cancer. *Eur J Surg Oncol* 2012; **38**: 497-502 [PMID: 22445061 DOI: 10.1016/j.ejso.2012.01.012]
- Greene FL. TNM staging for malignancies of the digestive tract: 2003 changes and beyond. *Semin Surg Oncol* 2003; **21**: 23-29 [PMID: 12923913 DOI: 10.1002/ssu.10018]
- Nitta T, Sato Y, Ren XS, Harada K, Sasaki M, Hirano S, Nakanuma Y. Autophagy may promote carcinoma cell invasion and correlate with poor prognosis in cholangiocarcinoma. *Int J Clin Exp Pathol* 2014; **7**: 4913-4921 [PMID: 25197362]
- Wang W, Zhang J, Zhan X, Lin T, Yang M, Hu J, Han B, Hu S. SOX4 is associated with poor prognosis in cholangiocarcinoma. *Biochem Biophys Res Commun* 2014; **452**: 614-621 [PMID: 25181339 DOI: 10.1016/j.bbrc.2014.08.124]
- Park KW, Jung ES, Kim DG, Yoo YK, Hong TH, Lee IS, Koh YH, Kim JH, Lee MA. ERCC1 Can Be a Prognostic Factor in Hilar Cholangiocarcinoma and Extrahepatic Bile Duct Cancer, But Not in Intrahepatic Cholangiocarcinoma. *Cancer Res Treat* 2013; **45**: 63-69 [PMID: 23613672 DOI: 10.4143/crt.2013.45.1.63]
- Cai WK, Lin JJ, He GH, Wang H, Lu JH, Yang GS. Preoperative serum CA19-9 levels is an independent prognostic factor in patients with resected hilar cholangiocarcinoma. *Int J Clin Exp Pathol* 2014; **7**: 7890-7898 [PMID: 25550829]
- Dong ZR, Zhang C, Cai JB, Zhang PF, Shi GM, Gao DM, Sun HC, Qiu SJ, Zhou J, Ke AW, Fan J. Role of 5-hydroxymethylcytosine level in diagnosis and prognosis prediction of intrahepatic cholangiocarcinoma. *Tumour Biol* 2014; Epub ahead of print [PMID: 25480415 DOI: 10.1007/s13277-014-2900-2]
- Tian X, Wang Q, Li Y, Hu J, Wu L, Ding Q, Zhang C. The expression of S100A4 protein in human intrahepatic cholangiocarcinoma: clinicopathologic significance and prognostic value. *Pathol Oncol Res* 2015; **21**: 195-201 [PMID: 24985031 DOI: 10.1007/s12253-014-9806-6]
- Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, Muto T, Sasaki H, Urabe K, Sueda T. Perineural invasion in extrahepatic cholangiocarcinoma: prognostic impact and treatment strategies. *J Gastrointest Surg* 2013; **17**: 1429-1439 [PMID: 23797881 DOI: 10.1007/s11605-013-2251-0]
- Kulig J, Sierzega M, Kolodziejczyk P, Popiela T. Ratio of metastatic to resected lymph nodes for prediction of survival in patients with inadequately staged gastric cancer. *Br J Surg* 2009; **96**: 910-918 [PMID: 19591164 DOI: 10.1002/bjs.6653]
- Yu JX, Li Y. The staging system of metastatic lymph node ratio in gastric cancer. *Clin Oncol (R Coll Radiol)* 2007; **19**: 269-270 [PMID: 17433973 DOI: 10.1016/j.clon.2007.02.003]
- Marchet A, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, Roviello F, de Manzoni G, Minicozzi A, Natalini G, De Santis F, Baiocchi L, Coniglio A, Nitti D. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg* 2007; **245**: 543-552 [PMID: 17414602 DOI: 10.1097/01.sla.0000250423.43436.e1]
- Xu DZ, Geng QR, Long ZJ, Zhan YQ, Li W, Zhou ZW, Chen YB, Sun XW, Chen G, Liu Q. Positive lymph node ratio is an independent prognostic factor in gastric cancer after d2 resection regardless of the examined number of lymph nodes. *Ann Surg*

- Oncol* 2009; **16**: 319-326 [PMID: 19050970 DOI: 10.1245/s10434-008-0240-4]
- 27 **Kim CY**, Yang DH. Adjustment of N stages of gastric cancer by the ratio between the metastatic and examined lymph nodes. *Ann Surg Oncol* 2009; **16**: 1868-1874 [PMID: 19434459 DOI: 10.1245/s10434-009-0430-8]
- 28 **Tamandl D**, Kaczirek K, Gruenberger B, Koelblinger C, Maresch J, Jakesz R, Gruenberger T. Lymph node ratio after curative surgery for intrahepatic cholangiocarcinoma. *Br J Surg* 2009; **96**: 919-925 [PMID: 19591163 DOI: 10.1002/bjs.6654]
- 29 **Kawai M**, Tani M, Kobayashi Y, Tsuji T, Tabuse K, Horiuchi T, Oka M, Yamaguchi K, Sakata Y, Shimomura T, Yamaue H. The ratio between metastatic and examined lymph nodes is an independent prognostic factor for patients with resectable middle and distal bile duct carcinoma. *Am J Surg* 2010; **199**: 447-452 [PMID: 19596119 DOI: 10.1016/j.amjsurg.2009.01.019]

**P- Reviewer:** Andersson RG, Parsi MA, Pinlaor S, Plentz RR, Vegso G  
**S- Editor:** Ma YJ **L- Editor:** AmEditor **E- Editor:** Ma S





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045