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# Lymph node dissection in resectable perihilar cholangiocarcinoma: a systematic review

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**KEYWORDS:**
Perihilar cholangiocarcinoma;
Staging;
Lymphadenectomy;
Lymph node retrieval;
Lymph node number

**Abstract**

**BACKGROUND:** Perihilar cholangiocarcinoma is usually unresectable at the time of diagnosis. Only few patients are candidates for a potential curative treatment. For those patients, prognosis is strongly related to negative resection margin and lymph node status. Thus, a certain benchmark of lymph node count is necessary to secure relevant lymph node recovery and to avoid understaging. However, the required minimum number of retrieved lymph nodes remains unclear for perihilar cholangiocarcinoma. The 7th American Joint Committee on Cancer tumor, nodes, metastases edition increased the requirement for the histologic examination of lymph nodes in perihilar cholangiocarcinoma patients from 3 to 15. The applicability of such recommendation appears difficult and questionable. Therefore, the purpose of this systematic review is to evaluate the number of retrieved lymph nodes for staging of patients undergoing surgery for perihilar cholangiocarcinoma.

**METHODS:** The MEDLINE, EMBASE, and The Cochrane Library databases were systematically screened up to December 2014. All studies reporting the number of lymph node count in perihilar cholangiocarcinoma were included and assessed for eligibility.

**RESULTS:** A total of 725 abstracts were screened and 20 studies were included for analysis, comprising almost 4,000 patients. The cumulative median lymph node count was 7 (2 to 24). A median lymph node count greater than or equal to 15 was reported in 9% of perihilar cholangiocarcinoma patients and could only be achieved in extended lymphadenectomy. Subgroup analysis revealed a median lymph node count of 7 (range 7 to 9), which was associated with the detection of most lymph node positive patients and showed the lowest risk for understaging patients. Lymph node count greater than or equal to 15 did not increase detection rate of lymph node positive patients.

**CONCLUSIONS:** This systematic analysis suggests that lymph node count greater than or equal to 7 is adequate for prognostic staging, while lymph node count greater than or equal to 15 does not improve detection of patients with positive lymph nodes.



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Perihilar cholangiocarcinoma represents 60% of all types of cholangiocarcinoma and radical surgical resection remains the only curative approach.[1,2] Despite major development on surgical strategies over the past decades, reported 5-year survival rates after surgery remained poor (below 20%).[3]

Along with negative resection margins, the presence of lymph node metastasis represents the most significant prognostic parameter for perihilar cholangiocarcinoma.[4–6] A certain benchmark number of retrieved lymph nodes is necessary to secure a representative staging. However, this number varies much among specialized centers. An insufficient lymph node count may result in understaging of the disease. Consequently, poor recovery of lymph nodes may increase the rate of incorrectly classified N0 patients, overestimating the survival expectancy[7] This issue has been debated without reaching a consensus on the best approach.[7–10]

Indeed, the required extent of lymphadenectomy for perihilar cholangiocarcinoma remains controversial. The latest tumor, nodes, metastases (TNM) edition has triggered criticisms by experts. While for the first time the 7th AJCC (American Joint Committee on Cancer) TNM edition adequately separated extrahepatic cholangiocarcinoma into 2 distinguished groups as perihilar and distal tumors, it also increased the requirement for the histologic examination of lymph nodes from formerly 3 to 15 lymph nodes.[11] A number of retrospective studies have addressed this topic and lead to the recommendation of more conservative recommendations for the recovery of lymph node count.[12–15] The aim of this study was to review the existing literature examining the number of retrieved lymph nodes in resected perihilar cholangiocarcinoma patients offering the best prediction of patient survival and to attempt to provide evidence for a potential recommendation of lymph node count.

## Methods

### Search strategy

A systemic electronic searched for studies published until December 2014, screening different databases as MEDLINE, EMBASE, and Cochrane. This search was conducted using the following terms: (Perihilar cholangiocarcinoma OR Cholangiocarcinoma OR Klatskin* OR Hilar Cholangiocarcinoma) AND (Lymphadenectomy OR Lymph node metastases OR Lymph node retrieval OR Lymph node number OR Lymph node count OR Lymph node ratio).

### Inclusion and exclusion criteria

All studies reporting resected perihilar cholangiocarcinoma patients with a number of retrieved lymph nodes were included. Studies with various entities were included, if subgroup information about perihilar cholangiocarcinoma populations was provided. Abstracts, reviews, case reports, letters to the editor, and articles available in non-English language were excluded from analysis.

### Data extraction

The following data were extracted: study period, number of patients, age, cancer entity, characteristics of resection (liver resection or bile duct resection and additional procedures as pancreatoduodenectomy), type of lymphadenectomy (extended vs regional), histopathological information (TNM classification, number of lymph node retrieval, number of positive lymph nodes), and clinical outcomes (median survival and 1, 3 [data not shown], and 5-year survival). The extent of lymphadenectomy was adopted according to the classification of the Japanese Society of Biliary Surgery[16]: Regional lymphadenectomy includes nodes around the cystic duct, pericholedochal, periportal, and surrounding the hepatic artery while additional celiac trunk, superior mesenteric, and paraortic lymph node dissection is considered as extended lymphadenectomy.

Two independent reviewers (P.K. and M.L.) screened all articles and checked extracted data for accuracy.

### Statistical analysis

The total lymph node count was reported as median and range, as described by the majority of included publication. The distribution of variables for non-normally distributed data is expressed using medians and interquartile ranges (IQR). The Mann–Whitney $U$ test or the one-way analysis of variance tests was used. Spearman's rank correlation was computed among continuous variables.

Because of the fact that point estimates from most of the studies (eg, odds ratios or risk ratios for binary outcomes, or mean difference for quantitative outcomes including 95% confidence interval) were missed, a statistical analysis by pooling the data according to the meta-analysis methods could not be performed.

Significance was set at $P$ value equal to .05 and statistical trend was defined as $P$ less than or equal to .1. Statistical analyses were performed with the software package SPSS 22 (SPSS, Inc, Chicago, IL) and GraphPad Prism Software Version 6.0.

## Results

### Search results

From all databases, 1,248 studies were identified through screening of MEDLINE (n = 548), EMBASE (n = 634), and Cochrane (n = 8). After deduplication, a total of 725 studies remained for abstract reviewing. Of these, 260 studies were excluded because of exclusively reporting a different cancer entity (ie, intrahepatic cholangiocarcinoma, distal bile duct, and gallbladder cancer),

and 56 were solely review articles. In the remaining search, 274 findings were case reports, letters, animal studies, or data reported in a different investigation field (ie, radiology). Finally, after critical reading of 135 articles, 20 studies were considered for the final analysis (Fig. 1).

## Descriptive cohort

A total of 20 studies reporting the number of recovered lymph nodes in resected perihilar cholangiocarcinoma patients were included. Overall, 3,986 patients with a median age of 66 years (range 58 to 70) were described and 2,128 patients (53%) suffered from perihilar cholangiocarcinoma (Table 1).[12–15,17–32] In addition, 11 studies reporting exclusively perihilar cholangiocarcinoma patients, provided 68% (n = 1,437) perihilar cholangiocarcinoma patients and 9 studies with heterogeneous entities, included 33% (n = 691) of perihilar cholangiocarcinoma patients. The heterogeneity of other tumor entities were described in 1,858 patients (47%) including ampullary cancer (n = 742, 19%), gallbladder cancer (n = 466, 12%), distal bile duct cancer (n = 372, 9%), intrahepatic cholangiocarcinoma (n = 74, 2%), middle bile duct cancer (n = 37, 1%), proximal bile duct cancer (n = 15, .4%), hepatocellular carcinoma (n = 75, 2%), and colorectal liver metastases (n = 77, 2%). Regarding the type of surgical treatment, detailed information about 2,835 (71%) surgical procedures was available. With 1,611 surgical procedures, liver resection was the most commonly reported surgery, of which 259 (7%) implicated a caudate lobectomy. Bile duct resections alone were likewise reported 259 (7%) times and 483 (12%) patients underwent additional procedure as pancreatoduodenectomy. Vascular resections were reported in 7% (n = 291) of the entire population. Table 2 displays the histopathological findings.

## The number of retrieved lymph nodes

The median number of lymph node count was reported in all 20 studies ranging from 2 to 24 lymph nodes (Fig. 2). In 60% of the studies (n = 12), exclusively regional lymphadenectomy was described. Consequent extended lymphadenectomy was performed in 2 studies only (Table 3). Further 5 studies described mixed populations of regional and extended lymphadenectomy, as strategies changed from extended to regional lymphadenectomy within the observational period. Extended lymphadenectomy was significantly correlated with increased median lymph node count ($P = .003$) and was performed more frequently if additional pancreatoduodenectomy was conducted in the study (5/10 vs 2/11 studies, $P = .102$). Of note, study populations including a subset of patients undergoing pancreatoduodenectomy observed higher median lymph node count (6, IQR 3.0 to 7.5 vs 11.5, IQR 7.5 to 13.8; $P = .034$), but no difference in median detection rate of lymph node positive patients (41.2, IQR 33.5 to 47.9 vs 40.0, IQR 39.4 to 43.8; $P = .912$).

The retrieval of 3 lymph nodes was the most commonly reported median lymph node count (5 studies,[12,21,26,28,31] n = 620, 29%), followed by the lymph node count = 7 (3 studies,[14,20,22] n = 134, 6%). Three studies[17,23]

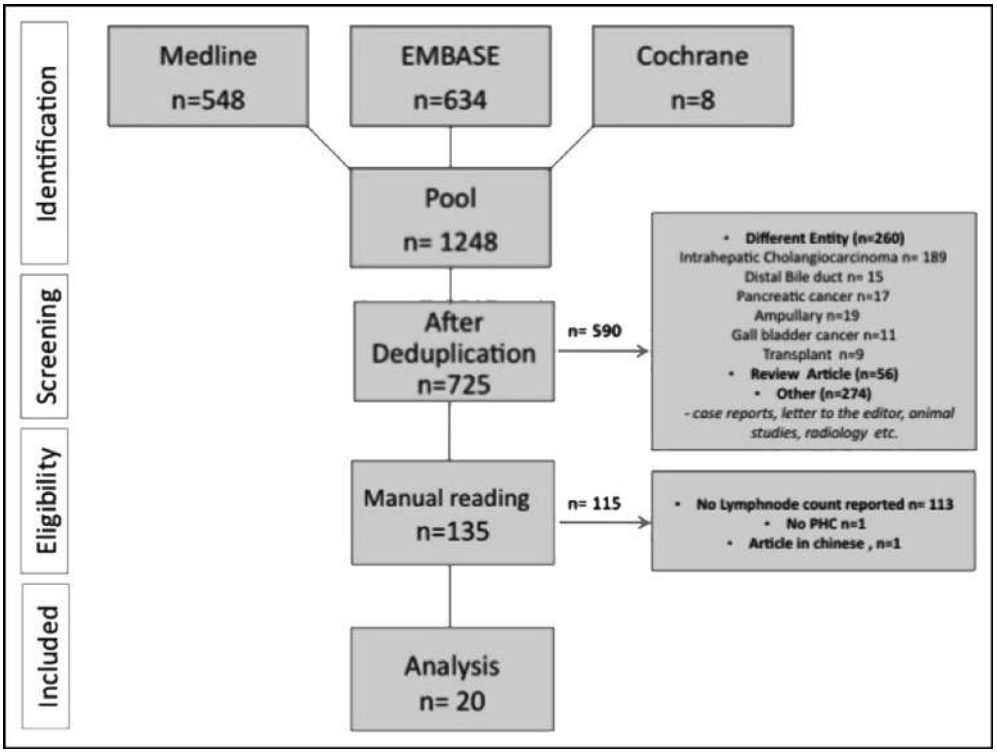


**Figure 1** Search and selection strategy flow chart.

**Table 1** Study characteristics and type of resection

| Author | Year | Period | Entity | n | Age (median) | Hepatic resection | Only BD resection | Combined PD |
|---|---|---|---|---|---|---|---|---|
| Kitagawa[17] | 2001 | 1983–1998 | PHC | 110 | 60 | 0 | 0 | 0 |
| Schwarz[18] | 2007 | 1973–2004 | exHBDCA | 393 | – | – | – | – |
| | | | Ampullary | 683 | | | | |
| | | | Gallbladder | 440 | | | | |
| Ito[12] | 2010 | 1987–2007 | PHC | 144 | 68 | 170 (64%) | 33 (12%) | 123 (46%) |
| | | | dBDCA | 113 | | | | |
| Kawai[19] | 2010 | 1991–2004 | mBDCA | 26 | 67 | 0 | 4 (7%) | 58 (94%) |
| | | | dBDCA | 36 | | | | |
| Ravaioli[20] | 2010 | 2001–2005 | exHBDCA | 10 | 66 | 162 | – | – |
| | | | HCC | 75 | | | | |
| | | | CRM | 77 | | | | |
| Rocha[21] | 2010 | 1991–2008 | PHC | 146 | 65 | 66 | – | – |
| Guglielmi[22] | 2010 | 1990–2008 | PHC | 62 | 66 | 54 (87%) | 8 (13%) | – |
| Murakami[23] | 2011 | 1992–2009 | PHC | 25 | 68 | 25 (100%) | 1 (4%) | 2 (8%) |
| | | | IHC | 6 | | 6 (100%) | – | – |
| | | | dBDCA | 31 | | – | – | 31 (100%) |
| | | | Gallbladder | 19 | | 7 (37%) | 6 (32%) | 6 (32%) |
| | | | Ampullary | 59 | | – | – | 32 (54%) |
| Murakami[24] | 2011 | 1990–2009 | PHC | 50 | 69 | 45 (90%) | 5 (10%) | 3 (6%) |
| | | | IHC | 21 | | 21 (100%) | – | – |
| | | | dBDCA | 56 | | – | – | 48 (86%) |
| Oshiro[25] | 2011 | 2001–2009 | PHC | 16 | 70 | 26 (43%) | 11 (18%) | 25 (42%) |
| | | | pBDCA | 15 | | | | |
| | | | mBDCA | 11 | | | | |
| | | | dBDCA | 18 | | | | |
| Patel[26] | 2011 | 2000–2009 | PHC | 34 | 66 | 65 (94%) | – | – |
| | | | IHC | 35 | | | | |
| Ruys[27] | 2011 | 1992–2010 | PHC | 147 | 62 | – | – | – |
| De Jong[28] | 2012 | 1984–2010 | PHC | 305 | 66 | 224 (73%) | 81 (27%) | – |
| Kow[29] | 2012 | 1995–2010 | PHC | 127 | 62 | 127 (100%) | – | 10 (8%) |
| Noji[30] | 2012 | 1997–2007 | PHC | 110 | 69 | 90 (82%) | 13 (12%) | 16 (15%) |
| | | | dBCA | 118 | | 15 (13%) | 16 (14%) | 93 (79%) |
| Aoba[13] | 2013 | 2000–2009 | PHC | 320 | 65 | 316 (99%) | 4 (1%) | 34 (11%) |
| Guglielmi[14] | 2013 | 1990–2008 | PHC | 62 | 66 | 55 (89%) | 7 (11%) | – |
| Ocuin[31] | 2013 | 2000–2008 | PHC | 19 | 62 | 30 (79%) | – | – |
| | | | IHC | 12 | | | | |
| | | | Gallbladder | 7 | | | | |
| Hakeem[15] | 2013 | 1994–2010 | PHC | 78 | 58 | 72 (92%) | 6 (8%) | 2 (3%) |
| Nari[32] | 2014 | 1998–2012 | PHC | 45 | 66 | 35 (78%) | 10 (22%) | – |

BD = bile duct; CRM = colorectal metastases; dBDCA = distal bile duct cancer; exHBDCA = extrahepatic bile duct cancer; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma; mBDCA = middle bile duct cancer; pBDCA = proximal bile duct cancer; PD = pancreatoduodenectomy; PHC = perihilar cholangiocarcinoma.

(n = 377, 18%) reported a median lymph node count over 15 according to the recommendation of the 7th AJCC edition. In these 3 studies, extended lymphadenectomy was the technique of choice (n = 312, 83%).

Combining all studies, the cumulative median number of lymph node count was 7 (IQR 3 to 11) (Table 3).

## Impact of lymph node count on lymph node detection rate and survival

The rate of lymph node positive (N+) patients ranged from 31% to 58% among the different publications (Table 2). The median lymph node count did not correlate with the rate of N+ patients ($P$ = .147), with the median amount of positive lymph nodes ($P$ = .683), with the 5-year survival rate ($P$ = .355), or with the median overall survival ($P$ = .842).

A subgroup analysis revealed that studies with a median lymph node count of 7 to 9 showed the highest detection rate of N+ patients. Again no impact on 5-year or median overall survival was documented (Table 4, Fig. 2A). Although this difference did not reach a statistical significance ($P$ = .265), the rate of N0 patients (46.6 ± 3.6, $P$ = .008) was significantly lower in the lymph node count 7 to 9 group (Table 4, Fig. 2B). Of note, the rate of

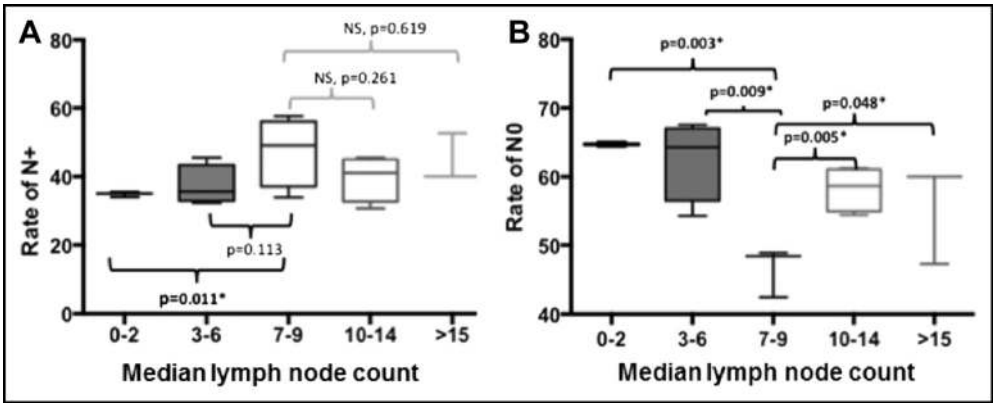


**Figure 2** Correlation of lymph node count and detection rate of N+ and N0. (A) Correlation of lymph node count and detection rate of lymph node positive (N+) patients; (B) correlation of lymph node count and rate of lymph node negative (N0) patients. Abbreviations: N+ = lymph node positive; N0 = lymph node negative patients; ns = nonsignificant.

advanced tumor stages T3/T4 did not differ significantly among the 5 subgroups ($P = .344$).

Referring to the 7th AJCC edition, a lymph node count greater than or equal to 15 was neither associated with an increased rate of N+ patients ($P = .540$) nor a reduction in N0 patients ($P = .665$) as compared with lymph node count less than 15. Likewise, a lymph node count less than or equal to 15 did not significantly influence 5-year survival ($P = .385$) or median survival ($P = .754$) rates.

## Comments

It is currently well accepted that a certain extent of lymphadenectomy is necessary in the surgical therapy of perihilar cholangiocarcinoma. Ravaioli et al[20] reported that lymphadenectomy improved 5-year survival from 16% to 31%, as compared with patients undergoing resections of perihilar cholangiocarcinoma without lymphadenectomy. Although earlier studies compared the type of lymphadenectomy,[17,33] namely extended vs regional, recent publications shifted their focus toward the required numerical lymph node count for a conclusive lymph node staging.[12,13,22] In this context, the latest TNM classification recommended a lymph node count greater than or equal to 15 lymph nodes, as a requirement for adequate lymph node staging. Since then, a wave of criticisms was perceivable among experts. This study is the first systematic review investigating the number of retrieved lymph nodes in resected perihilar cholangiocarcinoma patients.

**Table 2** Histopathological findings and survival

| Author | AJCC edition | T1/T2 | T3/T4 | N0 | N+ | R0 | Median survival | 5-year survival |
|---|---|---|---|---|---|---|---|---|
| Kitagawa[17] | 5th | 42 (38%) | 68 (62%) | 52 (47%) | 58 (53%) | – | – | 19% |
| Schwarz[18] | – | – | – | – | – | – | – | – |
| Ito*,[12] | 6th | 112 (44%)* | 143 (56%) | 168 (65%) | 89 (35%) | 212 (83%) | 25 | 34% |
| Kawai*,[19] | 5th | 46 (74%) | 16 (26%) | 38 (61%) | 24 (39%) | 48 (77%) | | 43% |
| Ravaioli*,[20] | – | – | – | – | – | 66 (100%) | – | 24% |
| Rocha[21] | 6th | 89 (76%) | 29 (25%) | – | – | 48 (41%) | – | – |
| Guglielmi[22] | 7th | – | – | 41 (66%) | 21 (34%) | 46 (74%) | 22 | 15% |
| Murakami[23] | 7th | – | – | 15 (60%) | 10 (40%) | 22 (88%) | 22 | 40% |
| Murakami[24] | 7th | – | – | 30 (60%) | 20 (40%) | 37 (74%) | 22 | 37% |
| Oshiro*,[25] | 6th | 26 (43%) | 34 (25%) | 34 (57%) | 26 (43%) | 34 (57%) | – | 19% |
| Patel[26] | 7th | – | – | 23 (68%) | 11 (32%) | 53 (77%) | 22 | – |
| Ruys[27] | – | – | – | 93 (63%) | 54 (37%) | – | – | – |
| De Jong[28] | – | 87 (29%) | 131 (43%) | 166 (54%) | 139 (46%) | 197 (65%) | | 20% |
| Kow[29] | 7th | 92 (73%) | 35 (29%) | 77 (61%) | 39 (31%) | 112 (88%) | 49 | 48% |
| Noji[30] | 7th | 46 (42%) | 64 (59%) | 71 (65%) | 39 (36%) | 94 (86%) | – | 40% |
| Aoba[13] | 7th | 124 (39%) | 196 (61%) | 174 (55%) | 146 (46%) | 258 (81%) | – | 49% |
| Guglielmi[14] | 7th | – | – | 30 (48%) | 32 (52%) | 46 (74%) | 22 | 15% |
| Ocuin*,[31] | 7th | 20 (53%) | 17 (45%) | – | – | 28 (74%) | 17 | 7% |
| Hakeem[15] | 7th | 36 (46%) | 42 (54%) | 33 (42%) | 45 (58%) | 46 (59.0%) | – | 26% |
| Nari[32] | 7th | 22 (49%) | 21 (47%) | 22 (49%) | 21 (47%) | 27 (60.0%) | 31 | 21% |

AJCC = American Joint Committee on Cancer; N0 = lymph node negative; N1 = lymph node positive; R0 = tumor-free resection margin.
*Information for all entities included.

**Table 3** Numerical lymph node count

| Author | Type of LAD | Lymph node station* | Median LNC | Minimum LNC | Maximum LNC | Median positive | Recommended LNC |
|---|---|---|---|---|---|---|---|
| Kitagawa[17] | Ext | 8a/p, 9, 12a/b/c/h/p, 13a, 14 + 16 in ext. LAD | 24† | – | – | 3.4† | – |
| Schwarz[18] | Reg. + Ext. | – | 5 | 1 | 37 | 0 | 10 |
| Ito[12] | Reg. | 12a/b/h/p | 3 | 0 | 16 | 1 | 7 |
| Kawai[19] | Reg. | 12a/b/h/p, 14 | 12 | 5 | 38 | – | 12 |
| Ravaioli[20] | Reg. | 8a, 8p, 12a/b/h/p | 7 | 4 | 26 | – | – |
| Rocha[21] | Reg. | – | 3 | 0 | 16 | – | 7 |
| Guglielmi[22] | Reg. | – | 7 | 1 | 25 | – | 3 |
| Murakami[23],‡ | Ext. | – | 21 | 4 | 107 | – | – |
| Murakami[24],‡ | Reg. + Ext. | 8a/p, 12a/b/h/p, 13a +16 in ext. LAD | 16 | 1 | 64 | 3 | – |
| Oshiro[25],‡ | Reg. | 8a/p, 12a/b/h/p, 13a | 13 | 0 | 57 | – | 12 |
| Patel[26] | Reg. | – | 3 | 0 | 24 | 0 | – |
| Ruys[27] | Reg. + Ext. | – | 5 | – | – | – | 2 |
| De Jong[28] | Reg. | – | 3 | 1 | 22 | 3 | – |
| Kow[29] | Reg. | 8a/p, 9, 12a/b/h/p | 11 | 0 | 42 | 0 | – |
| Noji[30] | Reg. | 8a/p, 9, 12a/b/h/p | 2 | 1 | 8 | | |
| Aoba[13] | Reg. + Ext. | 8a/p, 12a/b/h/p, 13a + 16 in ext. LAD | 11 | 1 | 59 | – | 5 |
| Guglielmi[14] | Reg. | 8a/p, 12a/b/h/p, 13a | 7 | 1 | 25 | – | 7 |
| Ocuin[31] | Reg. | – | 3 | 1 | 16 | – | 7 |
| Hakeem[15] | Reg. + Ext. | 8a/p, 9, 12a/b/c/h/p, 13a, 14 + 16 in ext. LAD | 9 | 0 | 58 | 2 | 20 |
| Nari[32] | – | – | 9 | 4 | 27 | 1 | – |
| Cumulative | Median (IQR) | – | 7 (3–11) | 1 (0–1) | 27 (23–53) | 1 (0–2.5) | 7 (6–11) |

Ext. = extended; IQR = interquartile range; LAD = lymphadenectomy; LNC = lymph node count; Reg. = regional.

*Lymph node station according to Japanese Society of Biliary Surgery.[16] 8a: Antero-superior LN along the common hepatic artery; 8p: Posterior LN along the common hepatic artery; 9: LN at the celiac trunk; 12a: LN at the hepatoduodenal ligament along the hepatic artery; 12b: LN at the hepatoduodenal ligament along the bile duct; 12p: LN at the hepatoduodenal ligament behind the portal vein; 12h: Hepatic hilum; 13a: LN Posterior superior portion of the pancreatic head; 14: Superior mesenteric artery LN; 16: Paraaortic LN.

†Average.

‡Information for all entities included.

In this systematic review of the literature, a median lymph node count greater than or equal to 15 was described in a minority of publications, that is, in only 9% of analyzed perihilar cholangiocarcinoma patients. Of note, a significant portion of this population underwent extended lymphadenectomy. Although the cumulative median of lymph node count among all 20 publications was 7, the most commonly reported lymph node count appeared to be lower with a number of 3, whereas many centers support recommendation of sampling 2 to 7 lymph nodes. An additional increase in required lymph node count, as recommended by the 7th TNM edition, would further restrict the number of patients meeting this criterion. Therefore, the need of lymph node count greater than or equal to 15 is questionable in perihilar cholangiocarcinoma patients.

A lymph node count below a certain benchmark may result in understaging of patients with falsely increased N0 rate by missing potentially tumor positive lymph nodes. Conversely, it is assumable that populations with a higher lymph node count describe higher detection rates of N+ patients, and concomitantly lower rates of N0. This phenomenon has been observed by several authors in different entities.[7,9] The analysis of this systematical review revealed that the subgroup of patients with a lymph node count of 7 to 9 (median 7) disclosed the highest detection rates of N+ and lowest rate of N0 patients.

Several publications have suggested improved survival for patients undergoing lymphadenectomy above a certain cutoff.[13,22,32] Guglielmi[22] et al and Aoba et al[13] investigated a subgroup of N0 patients with tumor-free resection margins (R0), and found similar survival benefit for lymph node count greater than or equal to 3 and greater than or equal to 5. This "N0 + R0" subpopulation is most prone to the bias of understaging, and missing tumor affecting lymph nodes because of an insufficient lymph node count may bias survival data. Described 5-year survival rates increased from 20% to 27%[22] and from 15% to 71%,[13] respectively, if these thresholds of lymph node count were respected. Interestingly, Aoba et al found that there is a limitation to the beneficial potential of lymph node count, and a further increase in lymph node recovery over 5 did not show additional improvement in predicting survival. Of note, the highest investigated cutoff for lymph

**Table 4** Impact of LNC subgroups on detection rate of lymph node positive patients and survival

| Subgroup | LNC 0 to 2 (n = 110) | LNC 3 to 6 (n = 1,160) | LNC 7 to 9 (n = 257) | LNC 10 to 14 (n = 489) | LNC ≥ 15 (n = 185) | *P* value |
|---|---|---|---|---|---|---|
| LNC | 1.5 (1.0–2.0) | 3.0 (3.0–5.0) | 7.0 (7.0–9.0) | 11.5 (11.0–12.8) | 21.0 (16.0–24.1) | <.001 |
| Positive LN | – | 1.0 (.0–2.5) | 1.5 (1.0–2.0) | .5 (.0–1.0) | – | .554 |
| Rate of N+ | 35.5 (35.0–36.0) | 36.0 (32.8–43.8) | 49.5 (37.3–56.5) | 41.0 (33.0–45.3) | 40.0 (40.0–53.0) | .265 |
| Rate of N0 | 64.5 (64.0–65.0) | 64.0 (56.3–67.2) | 48.5 (43.5–61.8) | 59.0 (55.0–61.0) | 60.0 (47.0–60.0) | .008* |
| Rate of T3/T4 | 58.5 (58.0–59.5) | 44.0 (29.5–53.3) | 50.5 (47.0–54.0) | 27.5 (25.3–53.) | 62.0 (62.0–63.0) | .344 |
| Survival (months) | – | 22.0 (17.0–25.0) | 22.0 (22.0–31.0 | – | 22.0 (21.5–22.5) | .319 |
| 5-year survival rate | 39.0 (38.0–41.0) | 21.0 (10.3–31.3) | 21.0 (15.0–25.0) | 39.5 (24.9–48.8) | 37.0 (19.0–40.0) | .729 |

Values are displayed as median and interquartile range.
LN = lymph nodes; LNC = lymph node count; N+ = lymph node positive; N0 = lymph node negative.

node count was 10, which still is clearly below the recommendation of the 7th TNM edition.

No significant impact of lymph node count on median survival or 5-year survival could be shown in our analysis. A reason for this observation relies to the nature of our stud, which does not allow an appropriate N0 + R0 subgroup analysis—the population with obviously the best prognosis. This goes along with the study by Nari et al,[32] who failed to identify a survival benefit based on the lymph node count cutoff 5 ($P = .132$) and 7 ($P = .427$) in the overall population of perihilar cholangiocarcinoma patients.

One of the limitations of this study derives from the quality of data being reported. Likewise, the exact region of retrieved lymph node could only be determined in 55% of the investigated studies. As raw data of the single publications are not available, all our analysis was based on the provided median lymph node count. Nevertheless, this is the only feasible strategy in the process of a systematic review. This approach, however, still allows a comparison of populations with different median lymph node count. Another limitation is that patient survival can be influenced by several variables (ie, chemotherapeutic treatment, radiation), which were poorly reported in the available publications. Further different qualities in the reporting of lymph node recovery (eg, size of lymph nodes,[27] extracapsular growth,[30] and lymph node ratio[13,15,22,25]) have been discussed in literature as prognostic parameters. Unfortunately, such detailed information is missing in our analysis. Moreover, this systematic review includes studies before 2010 reporting their results according to previous AJCC editions. Still the impact on the findings in this study remains low, as only a minority of authors used the 5th or 6th edition (Table 2).

This study has, however, certain strengths, including the systematical approach with completeness of publications postulating the numerical lymph node count in perihilar cholangiocarcinoma patients until December 2014. Additionally, this review brings important knowledge to the field, providing for the first time a cumulative median of lymph node count in patients undergoing surgery for perihilar cholangiocarcinoma.

Thus, this study demonstrates that the cumulative median of reported lymph node count is 7, a figure significantly lower than the minimum lymph node count of 15, as recommended by the 7th TNM edition. A lymph node count greater than or equal to 15 was rarely reported for perihilar cholangiocarcinoma patients, even in series reporting extended lymphadenectomy. Therefore, the feasibility of the 7th TNM edition requirement is questionable. Nevertheless, a certain benchmark is necessary for a qualitative lymph node staging. The subgroup with a median lymph node count of 7 (range 7 to 9) appeared to offer the highest detection rate of lymph node positive patients and the lowest rate of potentially understaged N0 patients. On the other hand, a lymph node count greater than or equal to 15 was neither associated with increased detection rates nor with survival benefit.

Given the abovementioned limitations, a clear recommendation cannot be stated based on our review. A more precise strategy would be the acquisition of detailed prospectively assessed patient information in a standardized reporting system. Such a registry was already initiated and can help to postulate clear recommendations based on multicentric experience (www.cholangioca.org).[34]

## Conclusion

This systematic analysis suggests that lymph node count greater than or equal to 7 is adequate for prognostic staging, while lymph node count greater than or equal to 15 does not improve detection of patients with positive lymph nodes.

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