

Lymph node evaluation in gallbladder cancer: which role in the prognostic and therapeutic aspects. Update of the literature

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Abstract. – OBJECTIVE: The widespread use of laparoscopy has changed the outcome of gallbladder cancer as a consequence of increasing referral and incidental discovering of earlier stages cancer. Nevertheless, GBC is still associated with a poor prognosis and lymphnodal involvement is a main prognostic factor, important both for staging and for evaluating surgery quality. No consensus exists about the extension of lymphadenectomy to be performed nor about contraindications to extensive resection. A review of literature was so designed to identify the actual role, extension and limits of lymphadenectomy.

MATERIALS AND METHODS: A search on Pubmed and Scopus has been performed using the following keywords: gallbladder cancer, gallbladder neoplasm, surgery, laparoscopy, lymphadenectomy to evaluate the prognostic and the therapeutic role of the lymphadenectomy in gallbladder cancer.

The retrieved articles were analyzed aimed to evaluate the impact of lymphectomy and of its extension on overall and disease free survival.

RESULTS: Although no consensus still exists over the extension of ideal lymphadenectomy, some points are already clearly established: a part from T1a neoplasms, that do not require further surgery, and T1b for which a regional lymphectomy (N1) is safe and mandatory, more advanced stages require a more aggressive surgery but the fate of paraortic nodal station is still under evaluation. In fact some Authors still believe that the involvement of these nodes determine a so poor prognosis to make uselessly risky their surgical aggression. Other Authors conversely, show that there is not any difference in survival, among node positive patients, between paraortic node positive and no paraortic node positive patients.

CONCLUSIONS: The prognosis of gallbladder cancer remains poor because in most patients the diagnosis is made at an advanced stage. Complete surgical resection provides the only curative treatment option in this disease. In order to improve long-term outcome, several surgeons have advocated aggressive

surgical resection, including major hepatectomy, pancreatoduodenectomy and extended lymphadenectomy. Even a para-aortic nodal disease shouldn't discourage from pursuing this objective.

Key Words:

Gallbladder cancer, Gallbladder neoplasm, Surgery, Laparoscopy, Lymphadenectomy.

Introduction

Gallbladder cancer (GBC) is one of the most common malignancies of the biliary tract¹⁻³, which often arises in the setting of persistent chronic inflammation. The widespread use of laparoscopic techniques has led to an increase in referrals for cholecystectomy. As a consequence, the incidental finding of GBC at an earlier stage has modified the outcome of this disease.

GBC is an incidental finding in 0.25%-3% of patients and almost half of these cases are occasionally discovered during or after laparoscopic cholecystectomy for benign disease, such as gallstones and their complications (47% in the series of Memorial Sloan-Kettering Cancer Centre, 50% in the series of Johns Hopkins Hospital)⁴⁻⁵.

However, GBC is still associated with a poor prognosis. As well as for other cancers, lymphadenectomy in GBC not only provides important staging information, but more importantly represents an independent prognostic factor for survival, within the same pT stage category⁶.

Lymphadenectomy is also an important tool to assess the quality of the surgical treatment, although controversies do still exist with regard to the extension of lymphadenectomy⁷. Moreover, there is still no consensus about the correct assessment of lymph node status, that could be established according to location, number of nodes retrieved or lymph node ratio (LNR).

Materials and Methods

In order to assess the actual sceneries of lymphadenectomy in GC treatment, a search on the PubMed and Scopus database has been performed crossing the key words “Gallbladder neoplasms”, “surgery”, “lymphadenectomy” limited to the English literature between 2003 and 2013. A search on abstracts or full text had lead to the exclusion of other not pertinent articles. For studies conducted by the same research institute at different times, the most recent and complete one has been included, unless different methods or endpoints or specific issues had been addressed, leading to include 30 papers.

The references of pertinent papers have been searched for other relevant articles.

Topographical Distribution of Lymph Nodes Metastasis in GBC

GBC spreads through different ways: direct, lymphatic, vascular and neural invasion. The most common route of dissemination is lymphatic diffusion. This is made easier by lymphatic vessels in both the muscular and subserosal layers of the gallbladder.

Through this path, neoplastic cells, even without apparent trans-mural invasion, often spread to the lymph nodes along the bile ducts.

Although cystic, pericholedochal and hilar lymph nodes are the first key station, the lymph node involvement tends to be highly variable.

In fact, GBC can spread directly to the second (peripancreatic, periduodenal, periportal and perihepatic lymph node) or third level (celiac, superior mesenteric artery and the para-aortic lymph nodes) along the perivascular soft tissue, according to the three pathways of lymphatic drainage proposed by Ito et al⁸: cholecysto-retropancreatic pathway (main pathway), cholecysto-celiac and cholecysto-mesenteric pathways (accessory pathways).

Kondo et al⁹ have explained the failure of the pancreaticoduodenectomy to control lymph node

metastases, by the direct lymphatic connections with the paraortic lymph node stations.

Paraortic lymph node involvement has been found in 10-15% of T2 tumors; therefore, they suggested an extended paraortic lymphadenectomy as a standard treatment of the gallbladder cancer with subserosal invasion.

Assessment of Lymph Node Status

Presently the 7th edition of American Joint Committee on Cancer (AJCC) (Table I)¹⁰ and the Japanese Society of Biliary Surgery (JSBS)¹¹ (Table II) subdivide the nodal status into four (NX, N0, N1, or N2) and five categories (N0, N1, N2, N3 and N4) respectively, according to the anatomical location of positive lymph nodes.

The 7th edition of AJCC¹⁰ classifies as N1 (regional lymph nodes) metastases to nodes along the cystic duct, the common bile duct, hepatic artery and/or portal vein. Instead periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes are classified as N2 (extraregional metastases).

On the contrary, for some author this topographical distribution doesn't represent a correct evaluation of the lymph node status because N2 involvement does not adversely influence the disease specific survival (DSS) as compared to N1 disease¹²⁻¹⁴.

In a recent study, Liu et al¹² reported any statistical difference between N1 node-positive patients (median survival time 18 months; 5-year survival rate, 12.90%) and N2 node-positive patients (median survival time 13 months; 5-year survival rate, 16.67%) ($p = 0.389$).

Moreover, patients with N2 lymph node metastasis can achieve a satisfactory survival if radical lymphadenectomy is performed. An involvement of retropancreatic or anterior pancreatic lymph nodes (13 and 17 according the JSBS) does not represent a contraindication to surgical excision, and radical lymphadenectomy and pancreaticoduodenectomy can be carried out together with liver resection^{13,16,17,18}.

Endo et al¹⁹ first suggested that the positive lymph node count (PLNC) better predicts the prognosis than topographical location. Also Sakata et al²⁰ found this correlation in patients undergoing an R0 resection.

Therefore, it seems that the number and not the location of positive lymph nodes independently determines the prognosis after resection.

However the use of the PLNC as the only prognostic factor might be biased by an inade-

Table I. N classification from TNM 7th Edition¹⁰.

NX	Regional Lymph nodes cannot be assessed
N0	No regional Lymph nodes metastases
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Table II. Japanese Society Of Biliary Surgery Classification of N stage¹¹.

N0	No lymph nodes metastasis
N1	Lymph nodes metastasis in the primary lymph node group, i.e. adjacent to the tumor and around the extrahepatic bile duct
N2	Lymph nodes metastasis in the secondary lymph node group, i.e. the regional lymph nodes which are in the hepatoduodenal ligament
N3	Lymph Node metastasis in the tertiary lymph node group, i.e. regarded as next to regional lymph node
N4	Lymph node metastasis in the fourth lymph node group, i.e. more distant than N3

quate number of lymph nodes retrieved or histologically examined which leads to the phenomenon of “stage migration”¹³.

Also no consensus has been reached about the minimum number of lymph nodes (LNs) required for adequate staging.

Although the 6th edition of the AJCC²¹ suggested a minimum of three LNs that need to be examined to clearly establish the pathologic nodal staging, two recent population-based studies, from the SEER database²² and from the Johns Hopkins’s Hospital’s experience²³, demonstrated that among patients with resectable GBC, only 5% to 6.9% underwent an “adequate” lymphadenectomy, with ≥ 3 LNs histologically evaluated.

Eventually in 2011, Ito et al¹⁴ on 122 patients undergone a portal lymph node dissection at the Memorial Sloan Kettering Cancer Center, reported a median total lymph node count (TLNC) of only 3 nodes.

The same authors independently suggested that retrieval and evaluation of at least six lymph nodes improve risk-stratification after resection in node-negative patients.

With a median follow up time of 23 months (range 1-173 months) for the entire cohort, survival of patients classified as N0 based on TLNC < 6 was significantly worse than that of N0 patients based on TLNC ≥ 6 . The former infact presented a median recurrence free survival (RFS) 22 months versus not reached ($p < 0.001$) and median disease specific survival (DSS) 42 months versus not reached ($p < 0.001$)¹⁴.

Also Negi et al¹⁵ reported a linear correlation between TLNC and positive LN count. Based on the magnitude of the log-rank test, cut-off value for optimal TLNC stratification for the entire cohort was determined to be 6 lymph nodes. Survival of patients with negative nodes (N0) based

on TLNC < 6 was significantly worse than that of N0 based on TLNC ≥ 6 (median DFS, TLNC ≥ 6 vs. TLNC < 6 : not reached vs 32.00 ± 4.80 months). Furthermore, Negi et al¹⁵ first found that lymph node ratio (LNR) is a more appropriate tool to stratify patients with regard to prognosis. LNR is of particular value in patients who cannot adequately be staged because of the limited number of lymph nodes retrieved. In these cases LNR will more accurately reflect the nodal status than the PLNC or the TLNC²⁴.

On the other hand, Liu et al¹³ recently reported a significant correlation between TLNC and DSS in node-positive patients which led to a better prognostic substratification of these patients.

In fact N+ patients with TLNC < 6 and TLNC ≥ 6 had a median DSS 15 months and 33 months respectively, $p < 0.001$).

TLNC is warranted not only for accurate staging, but represents also an important tool for assessing the quality of the surgical treatment and of pathologic examination²⁵.

Extension of Lymphadenectomy

Lymphadenectomy in GBC not only provides important staging information, but more importantly represents an independent prognostic factor for survival⁶.

However, controversy exists over the type of lymphadenectomy which may be performed.

Instead, for Tis (tumor *in situ*) and T1a (tumor invades lamina propria) GBC, cholecystectomy alone, without lymphadenectomy, is commonly considered sufficient²⁶⁻²⁹, although some authors reported a residual nodal disease in about 2.5% of T1a GBC³⁰.

For T1b (tumor invades muscular layer) we believe that wedge resection of the gallbladder bed (3 cm) with regional lymph node dissection (N1 lymph nodes: hilar, cystic, pericholedochal, perihepatic and periportal lymph nodes) is the best choice for treatment¹.

A more aggressive approach is advised for T2 (tumor invades perimuscular connective tissue without extension beyond the sierosa or into the liver) and T3 (tumor perforates the serosa, visceral peritoneum and/or directly invades the liver and or an adjacent organ or structure such as stomach, duodenum, pancreas or extraepatic bile duct point and not comma). In these more advanced stages. Comma and not point several authors recommend to perform anatomic hepatic resection (S4a + S5), bile duct resection and extraregional lymph node dissection (N2 Lymph

nodes: periduodenal, peripancreatic lymph nodes and lymph nodes around the inferior mesenteric artery, common hepatic and celiac artery)^{27,28}.

Some Japanese authors advocated the routine use of an extended lymphadenectomy including the para-aortic lymph nodes³¹.

In the experience from Mount Sinai Hospital³², in patients with T3 stage or higher treated with hepatectomies no mortality was recorded, achieving respectively 1-, 3- and 5-year survival rates of 71.4%, 28.6% and 14.3%. Radical lymph node dissection ($p = 0.03$), absence of perineural tumor invasion ($p = 0.03$) and patients' age < 70 years ($p < 0.01$) were non-independently associated with favorable prognosis in these patients. The success with this aggressive approach, that included the caudate lobe, more than 4 liver segments, or part of the extrahepatic biliary tree in the resection specimen could be due to the elimination of perineural metastatic spread.

Resection of the Common Bile Duct During Lymphadenectomy

Resection of the common bile duct performed at the time of lymphadenectomy is controversial³³⁻²⁵.

GBC has a strong tendency to invade the hepatoduodenal ligament both as perineural invasion and as lymph node metastasis, therefore lymph node dissection of the hepatoduodenal ligament should include, besides en bloc resection of the regional lymph nodes, the excision of the connective tissue around the portal and hepatic artery^{18,36}. But the dissection of the hepatoduodenal ligament implies a risk of inducing ischemic damage to the common bile duct, so that Shimizu et al³⁷ proposed routine resection of the extrahepatic bile duct to facilitate lymphadenectomy while avoiding common bile duct ischemia, and harvesting a larger number of lymph nodes. However, these benefits have not been confirmed in other studies^{34,35}.

Pawlik et al³⁸ showed that the median number of lymph nodes harvested at the time of lymphadenectomy was the same ($n = 3$), regardless of whether the common bile duct was or was not resected concurrently with the lymph node dissection ($p = 0.35$).

Araida et al³³ found that, in patients with advanced GBC without direct invasion of the hepatoduodenal ligament and/or of the cystic duct, bile duct resection did not improve either recurrence rate and overall survival. Further, it would expose the patients to the risk of complications of the bilioenteric anastomosis such as bile duct infections or stenosis.

As a consequence, bile duct resection is justified only when a positive involvement of the cystic duct margins is discovered either on the pathology specimen of the cholecystectomy or after a biopsy of the cystic duct at the time of the second operation^{27,34,35}. In fact, microscopic involvement of the cystic duct margin is associated with a residual and/or additional disease in the common bile duct in over one-third of the cases^{34,35}.

Peripancreatic Lymph Nodes

The presence of peripancreatic (head only) lymph node disease is not a contraindication to surgical excision, unless radical R0 resection is made impossible by the presence of distant, liver or peritoneal metastases, point and not comma. Such metastases should be ruled out by frozen section examination of every suspicious nodule on liver or peritoneal surface^{16,17,31,39,40}.

Therefore radical lymphadenectomy and pancreaticoduodenectomy can be carried out together with liver resection, the so called "hepatopancreatoduodenectomy"

Performing a so aggressive surgery requires that a direct invasion of the liver and pancreas or duodenum or extensive involvement of the peripancreatic lymph nodes exist, without apparent bile duct involvement^{9,16,17,31,39,40}.

Also multi-organ loco regional involvement are effective treatment for GBC with direct invasion of the adjacent organs (stomach, duodenum, pancreas, colon and liver), but only if potentially curative resection (R0) is feasible.

In these cases of multi-organ resection, given radical R0 resection, the long-term survival will depend on bile duct involvement^{16,17,31,39,40}.

In fact, if stromal invasion of the extrahepatic bile ducts is found, it is probable that hepatoduodenal ligament is already involved with a high incidence of residual tumor and poor outcome after surgery¹⁸.

The same poor prognosis has been described by The Memorial Sloan-Kettering study group²⁹.

The involvement of the hepatic arteries or of the superior mesenteric artery is a further factor precluding any potentially curative (R0) resection. As a matter of fact, the soft tissue around the preserved hepatic arteries or around the superior mesenteric artery is the primary site of residual tumor, therefore before starting a resection, the involvement of these structures should be meticulously assessed¹⁸.

Para-Aortic Lymph Nodes

Previous reports concerning lymphatic diffusion pattern have shown that gallbladder cancer initially spreads to the nodes in the hepatoduodenal ligament, and eventually to the para-aortic lymph nodes through the retropancreatic nodes or the nodes around the common hepatic artery^{7,41}.

Therefore approximately 19% of patients with carcinoma of the gallbladder will present with para-aortic lymph nodes involvement⁴².

However, no consensus there is about the prognostic impact of these lymph node metastases and whether the involvement of this station is a contraindication for radical resection.

Survival studies after extended lymphadenectomy including para-aortic station have given controversial results, so that no consensus exists about the prognostic significance of these nodes involvement or whether it should be considered preclusive for a radical resection.

In their experience, Kondo et al⁴¹ reported no survival benefit from the routine use of an extended para-aortic lymphadenectomy in patients with paraaortic disease. These patients had a poor prognosis as those with distant metastases. Therefore, they concluded that a sample biopsy of para-aortic nodes should be performed before starting a radical resection, because they are involved more frequently than expected⁴¹.

On the contrary, some authors reported cases of gallbladder carcinoma with para-aortic lymph node metastasis with a long survival after an extended radical operation.

Murakami et al³¹ recently reported no significant difference in survival between patients with or without metastatic para-aortic lymph node, among all patients with nodal involvement ($p = 0.614$).

The 5-year survival rates of node-negative patients, node positive patients without para-aortic lymph node metastasis, and node-positive patients with para-aortic lymph node metastasis were 72, 31, and 24%, respectively. Median survival time of node-positive patients without para-aortic lymph node metastasis and node-positive patients with para-aortic lymph node metastasis were 14.3 and 14.7 months, respectively³¹.

Therefore survival of patients with para-aortic lymph node metastasis appears similar to that of node-positive patients without para-aortic lymph nodes involvement

Finally, by multivariate analysis, the authors proved that para-aortic lymph node metastasis was not an independent prognostic factor among

all patients and among patients with nodal positive involvement³¹.

We believe that para-aortic lymph node metastases is not a contraindication for radical resection of gallbladder cancer; the positive detection of metastatic para-aortic lymph nodes, during the preliminary pathological examination shouldn't prevent from performing an aggressive surgical procedure and achieving a radical resection.

No consensus exist on a worse prognosis for patients with para-aortic lymph node involvement compared to patients without such node metastases, therefore surgeons should not abandon the primary goal of surgery, radical resection (R0 resection), because long-term survival is possible in some cases^{43,44}.

Radical resection (R0 resection) with lymph node dissection and adjuvant chemotherapy is mandatory to improve survival of node positive patients with gallbladder cancer.

Conclusions

The prognosis of gallbladder cancer remains poor because in most patients the diagnosis is made at an advanced stage. Complete surgical resection provides the only curative treatment option in this disease. In order to improve long-term outcome, several surgeons have advocated aggressive surgical resection, including major hepatectomy, pancreatoduodenectomy and extended lymphadenectomy. Even a para-aortic nodal disease shouldn't discourage from pursuing this objective.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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