

Survival of Gallbladder Cancer with Infiltrative Node Beyond the Hepatic Pedicle

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Abstract

Gallbladder cancer is very lymphophilic and this feature remains one of the leading bad prognostic factors. To achieve a radical character in liver resection surgery more or less extended needs to be associated with lymphadenectomy. Lymphadenectomy interesting the hepatic pedicle is the most done technic. Few surgeons perform extended lymphadenectomy realize extended lymphadenectomy to remove a maximal lymph especially the node beyond the hepatic pedicle with a hope to ameliorate the prognosis of disease. We have adopted extended lymphadenectomy and we report long terms results for the patients who presented infiltrative node above the hepatic pedicle in view of survival at 5year. Patient and method: We report all patients operated on for gallbladder cancer and benefited from extended lymphadenectomy. Two hundred and four patients benefited from extended lymphadenectomy. One hundred had no node infiltration and 104 had node infiltration. Between these 104 patients, 68/104 (65,4%) had infiltrative node above hepatic pedicle. A total number of nodes was 1172 with mean of 17,5nodes per patient (03-36nodes) and ratio of infiltrative nodes was 31,5%. For pT1, pT2, pT3 and pT4, the percentage of infiltrative nodes was respectively 00%, 03%, 45,6% and 51,4%. Nighty-seven percent of infiltrative nodes were for pT3 and pT4. N1, N2 and N3 were distributed are follow: 36 (34,6%), 39 (37,5%) and 29 (27,9%). The morbidity and mortality were 32,5% and 13,5%. Three and 5-year survival rate were 20,5% and 10,3% for the entire series and 30,6% and 16,3% for R0 resection. Conclusion: Patients with infiltrative nodes behind hepatic pedicle do not have a worse prognosis in all cases. Radical surgery with extended lymphadenectomy must be carefully realized when R0 resection can be achieved for patient fit for aggressive surgery.

Keywords: Gallbladder Cancer; Extensive Lymphadenectomy; Global Survival; Infiltrative Nodes

Introduction

Gallbladder cancer is very lymphophilic [1] and this feature remains one of the leading bad prognostic factors [2]. To achieve a radical character in liver resection surgery more or less extended to one or more adjacent organs is necessary but not sufficient. This radical resection requires lymphadenectomy [3] with hepatic resection. Few surgeons make the extended lymphadenectomy retrieve a great number of lymph node and especially those localized beyond hepatic pedicle. The goal of its practice is an improvement of the prognosis. Some authors perform a lymphadenectomy of the common hepatic artery and reverse duodenopancreatic [4]. Only the Japanese authors go to achieve a lymphadenectomy of the inter-aorto-cellar area. In the West, the presence of lymph node infiltrated in inter-aorto-cave area are considered as distant metastases and contre-indicate radical resection [5-7]. The patients with

infiltrated lymph node in inter-aorto-caval have a poor prognosis by contribution to those who are free. It is the same for those with infiltration of the lymph nodes at the common hepatic channel and the celiac trunk [8]. Since the 1997 and 1988 classifications of the UICC and AJCC and various subsequent updates, reaching beyond the pedicle are considered as distant metastasis and resection is contraindication of radical surgery [9-10]. We have adopted over twenty years conducting extensive lymphadenectomy during radical surgery of gallbladder cancer on a routine basis. In this series of extensive lymphadenectomy, the reality of lymph node involvement beyond the hepatic pedicle proved common. The aim of this study is to know if an extended lymphadenectomy can achieve 5-year survival for patients with infiltrative lymph nodes beyond hepatic pedicle.

Patients and method

The radical surgery for gallbladder cancer in our daily practice fellow these ways: hepatectomy type IV-V bisegmentectomy for all tumors classified pT2, pT3 and pT4. The extent of this hepatectomy is suitable for locoregional invasion met the patient. In a first period, the tumors classified pT1a PT1b and were treated by a simple cholecystectomy without lymphadenectomy. Since 5years, the pT1b tumors are treated by IV-V bisegmentectomy. The extensive lymphadenectomy is performed from the hilum until inter-aorto-caval area in combination with hepatectomy or the reverse. It is performed as follows: removal of all nodes of the hepatic pedicle, followed by that of the common hepatic artery and the right side of the celiac trunk, followed by the posterior surface of duodenopancreatic block and inter-area aortico- cellar. In some cases, removal of lymph nodes in the superior mesenteric artery, those of gastroepiploic right group, the mesocolon, and splenic artery is performed according to the extension of the resection gesture dictated by the tumor extension. Radical surgery is successful in patients classified ASA I, II, III (without associated visceral disease with tare controlled or in some cases with associated disease well controlled before surgery) without diffuse liver and peritoneal metastases, absence of pulmonary metastases.

Lymph and lymph node relay gallbladder cancer are defined in the following way:

- N1: Lymph nodes and the liver pedicle (neck ganglion or Mascagni node, biliary duct node, portal vein node, lymph nodes in the proper hepatic artery (Figure 1)
- N2: lymph and retro-duodeno-pancreatic lymph nodes and those of the common hepatic artery. (Figure 2)
- N3: lymph nodes and the celiac trunk (right flank) and those of the inter-aorto-cellular area.

Figure 1: Close view.

Figure 2: Hepatic pedicle dissected with nodes removed, Distant view.

For some patients resected lymph nodes may be well beyond these areas (nodes of the superior mesenteric artery, those of gastroepiploic right group, the mesocolon, and the spleen artery). All patients underwent surgery and who received extensive lymphadenectomy and whose histological study showed an infiltration beyond the hepatic pedicle were included in the analysis. In our practice, pancreatoduodenectomy resection is the deduction for a patent visceral invasion or ineradicable nodes, which need this resection for total node ablation. Each group of nodes is fixed in formalin in a bottle apart after dissection outside of the surgical field by the surgeon. Each bottle is labeled and set apart as the main operating room. The samples are sent for histological analysis. Histological study was performed by the technique of hematoxylin-eosin and immunohistochemistry study technique was not be not used in this study. The parameters studied were:

- Preoperative and histological parameters: age, sex, associated disease, macroscopic tumor histological type, pTNM, TNM stage, the number of lymph nodes resected relay and patients, the total number of resected lymph nodes, the ratio of infiltrated nodes, presence of perineural infiltration, the presence of vascular emboli.
- Postoperative complications: vascular wounds, bile duct injuries, ..., and postoperative mortality and its cause.
- Long terms parameters: prescription of adjuvant chemotherapy, recurrence and places, treatment of recurrence and survival at 3 years and 5 years.

Results

Two hundred thirty-nine patients 204 have benefited from extended lymphadenectomy. There were 180femeles and 24males with mean of age of 58years (26 - 83years). A total of 1172nodes were resected with a mean per patient of 17,5 nodes (03-54nodes).

The mean nodes per patient level was 06 (01 – 20nodes) and ratio of infiltrative nodes was 31,6%. One hundred patients were N0, 36 N1, 39 N2 and 29 N3. 68 (65,4%) had infiltrative node beyond the hepatic pedicle. Regarding for pT1, pT2, pT3 and pT4, percentage of infiltrative node were respectively 00%, 03%, 45,6% and 51,4% (Table 1). The most infiltrative relay were neck node, bile duct nodes, portal vein nodes, common hepatic artery node and retro-duodenopancreatic nodes (Table 2). The morbidity and mortality were respectively 32,5% and 13,5%. Global 3 and 5year survival for the entire series are 30,6% and 16,3% for the R0 resection and out of postoperative mortality (Table 3).

Sex:	
Females	180
Males	24
Age	58years (26-83years)
All nodes resected	1172
Mean of node per patient	17,5 (03-54)
Mean of nodes per level	06 (01-20)
Ratio of infiltrative nodes	31,6%
Level of lymph infiltrated	
N0	49 % (100/204)
N1	34,6% (36/104)
N2	37,5% (39/104)
N3	27,9% (29/104)
N2 + N3	65,4% (68/104)
Infiltrated node according to T	
T1 : 00	00
T2 : 2/68 (3%)	03% (N2 : 1 and N3 : 1)
T3 : 31/68 (45,6%)	45,6% (N2 : 19 -N3 : 12)
T4 : 35/68 (51,4%)	51,4% (N2 : 19 - N3 : 16)

Table 1: Patients characteristics.

Morbidity	66		32,5%	
Mortality	28		13,5%	
Survival	N2		N3	N2+N3
Global (R0-R1-R2+postoperative mortality)	3years	10/39 (25,6%)	4/29 (13,8%)	14/68 (20,5%)
	5years	4/39 (11,5%)	3/29 (10,3%)	7/68 (10,3%)
R1+R2* + Mortality excluded	3years	11/31 (35,5%)	5/18 (27,8%)	15/49 (30,6%)
R0 and out of post-operative mortality	5years	5/31 (16,1%)	4/18 (16,7%)	8/49 (16,3%)

Table 2: Relay of infiltrative nodes.

Relay of nodes	Number of infiltrative nodes	%
Neck node (Mascagni)	16/17	94,1
Bile duct node	24/34	70,5%
Proper hepatic artery	14/37	37,8%
Portal vein	34/43	79%
Rétro-duodéno-pancreatic	41/47	87,2%
Common hepatic artery	31/53	58,5%
Inter-aortico-cave	23/58	38,6%
Coeliac trunk	6/26	23%

Table 3: Morbidity, mortality and 3 and 5year survival.

*: There is no survival beyond 18months for R1-R2 (mean survival 10,5mois (4 – 18mois)
R0: none residual tumor
R1: microscopic residual tumor
R2: macroscopic residual tumor.

Discussion

The lymph node is an important reality in the surgery of gallbladder cancer. Ogura., *et al.* [1] published the results of a multicenter study in 1991 involving 1686 cases of resection. The lymphatic and lymph node involvement were respectively 3.5% to 84.8% and from 2.5% to 74.4% starting from the purely mucous tumor that touching and exceeding the serous. This means that this attack is real, constant and frequent. In this series, the overall achievement of 51% and lymph node involvement beyond the hepatic pedicle is 65%. The counts reported in the literature are greater than 50% and can reach the same rate of 73% [8]. For lymph node infiltration beyond the hepatic pedicle, Yamaguchi [11] reported a rate of 28.5% in N1, N2 to 17% and 18.6% in N3. For Kondo [8], lymph node involvement was 73% in N1 and N2 and N3 38%. Some authors have reported pure nodal recurrences in inter-aorto-cellar in patients who received only a limited lymphadenectomy diagnosed purely nodal recurrences in inter-aorto-cellar and even in the renal pedicle right after surgery radical [12,13]. It seems given the Japanese series more lymphadenectomy is extended to the inter-aorto-cellar area, most are found infiltrated nodes. On the other hand, over the parietal extension is important (to the serous and beyond), the more of involved lymph nodes and infiltration that goes to the N3 level. Our series is exactly that with a rate of 97% for pT3 tumors and pT4 with lymph node infiltration N2 and N3. It is for us the first criterion that makes us remember his indication. If all authors are unanimous in saying that patients without lymph node infiltration have an oscillating interesting survival depending on the series ranging from 25% to 94.4% [11,13-17], others went up against a state-curative resection before a cancer of the gallbladder with lymph node infiltration tout court [18]. Others report interesting results for a limited interference with the hepatic

pedicle [11,19,20]. Among patients with lymph node infiltration, it is clear that only the hepatic pedicle does not seem very pejorative. In our series, survival at 5 years for a limited interference with the hepatic pedicle is 56% (data not shown). When infiltrative nodes exist beyond the hepatic pedicle, the survival rate at 5 years fall in a major way. Kondo, *et al.* [8] reported a zero-survival rate in patients with lymph node infiltration in inter-aorto-cellar in a series of 60 patients who underwent extensive lymphadenectomy. For Chijiwa [19] when a resection with lymphadenectomy is performed and only the hepatic pedicle nodes are invaded (N1), this portends a good prognosis. The same author reported a 5-year survival rate of 28% in patients with lymph node infiltration N2 [21]. In the series reported by Onoyama [11], 5-year survival rate was 68.7%, 60% and 28.6% respectively for N0, N1 and N2. Some authors [22,23] are going to associate a pancreatoduodenectomy resection for cleaning as they think that this side of the surgery has its importance in the achievement of optimal surgical faces of cancer of the gallbladder. But could this extensive lymphadenectomy routinely executed justify by a gain in survival at 5 years in the face of risks to the patient? It is reported in recent years either isolated cases or small series of patients with lymph node infiltration in inter-aorto-caval alive beyond 3 years and 5 years. We report (Table 5) patients with long survival and lymph node infiltration in inter-aorto-cellar. The most important experience is that of Murakami [23] reported a series of 113 cancers of the biliary tract (56 bile duct cancers, 6 peripheral cholangio carcinome, 32 ampuloma and 19 cancer of the gallbladder). Of the 17 cases of infiltration in inter-aorto-area, 3 concerned the gallbladder cancer. Overall 5-year survival for all etiologies is 24%. For this team, lymphadenectomy is justified only when the nodes are not pathological macroscopically. In the opposed figure (macroscopically infiltrated nodes) the resection is contre-indicated because there the 5-year survival year rate is nil. In our opinion, it is justified to perform an extensive lymphadenectomy for the following reasons:

1. Lymph node infiltration beyond the hepatic pedicle is the one that prevails and does not realize what is left in place in average half the nodes infiltrated into place. There are two-thirds of infiltrated nodes of patients in our series (65.4%).
2. The second relay damage (N2) and that of the third relay (N3) have the same survival at 5 years and therefore requires the completion of lymphadenectomy to levels every 2 simultaneously. In other words, realize the second relay without third is running the risk of letting up infiltrated nodes. Kondo [8] shows that cases classified N0 or N1 + only are free from infiltration N3 (inter-aorto-cellar). Conversely, if the infringement affects the second level (N2 +), 67.7% of patients at this stage have positive nodes N3 (inter-aorto-caval).
3. Achieving this extensive lymphadenectomy is set to present the most accurate classification for the patient.
4. It is very possible that this extensive lymphadenectomy is itself a therapeutic value by the maximum extirpation of nodes in the patient. In our series, the average number of nodes is 17,5 ganglions. In the literature, this ranges from 6 to 22 [8, 25, 26, 27] (Table 4). We must remember that 97% of our patients with lymph node infiltration beyond the hepatic pedicle had a pT3 tumor or pT4 and that is that when the surgeon is addressing the tumors who are the majority, he must go as far as possible in this lymphadenectomy. Some patients with pT2 and pT3 tumors (tumors confined to the bladder) macroscopically considered as good candidates have infiltrative nodes beyond the hepatic pedicle. They represent 45.6% of this series and all the problems is to achieve extirpation of nodes to properly classify and have therapeutic value. At present and in our view the 5-year limit of the bar can be a hard limit to achieve in these patients and a 3-year survival may prove as a worthy goal in this series where it is 28.6%. Murakami, *et al.* [23] and Yonemori, *et al.* [30] reported prolonged survival in patients with tumors of the bile ducts demonstrating that prolonged survival as well as for cancer of the gallbladder as the rest of the tract cancers bile (Table 5). In fact, it must be very vigilant in the indication of this extensive lymphadenectomy to the extent that we must respect the following:
 1. The risk of moderate or minimal morbidity and near zero mortality has to be the goal for the surgeon. We must point that our morbidity and mortality are high. It is our future challenge that we have to reach for decreasing them, ameliorate the postoperative results and then the long terms survival.
 2. Insurance to achieve a R0 resection. We have no survival at 3 years for R1 and R2 resection.
 3. Do not forget that if at present there is no standard treatment for postoperative against the gallbladder cancer. The presence of infiltrated nodes is a situation requiring adjuvant therapy given rate survival. So, this extensive lymphadenectomy allows doing the choice of a future effective adjuvant therapy.
 4. Finally, we must not lose sight of the difficulties of achieving lymphadenectomy and especially vis-à-vis the proper hepatic artery and operative length generated by its practice. About 70% of operating time is devoted to the realization of extensive lymphadenectomy in our experience.

Author	Year	Number Of Patient	Global Reach	N0	N1	N2	IAC -CT - SMA
Tsukada	1997	111	54%	46%	21,7%	31,5%	31,5%
Shimada	1997	41	63,4%	35,6%	36,6%	51,2%	17%
Noie	1999	41	34,2%	65,8%	34,2%	19,5%	9,8%
Kondo	2000	60	73,3%	26,7%	16,6%	56,6%	38,3%
Shirai	2002	135	44%	56%	18%	26%	-
Ryoko	2005	65	41,5%	58,5	-	-	23,1%
Present series	2016	204	56,9%	43,1%	33,3%	16,1%	16,7%

Table 4: Infiltrative node and relay in the literature.

IAC: inter aortico-cave.

CT: celiac trunk.

SMA: superior mesenteric artery.

Author	Year	Number of patients	Tumour location	N	Survival
Araida	1993	1	Gallbladder	N3	36months
Shirai	1995	3	Gallbladder	N2	4yaers – 6years -3,5years
Shinkai	1996	1	Gallbladder	N3	84months
Ijichi	1996	1	Gallbladder	N3	77months
Endo	1996	1	Gallbladder	N3	60months
Tsukada	1997	4	Gallbladder	N3	Survival beyond 60months
Kurokawa	1999	1	Gallbladder	N3	39months
Kondo	2001	1	Gallbladder	N3	69months
Miyasaki	2004	1	Gallbladder	N3	66months
Sasaki	2004	5	Gallbladder	N3	3/5 survival beyond 60months
Tokuyama	2005	1	Gallbladder	N3	43months
Sakata	2007	1	Gallbladder	N3	77months
Yonemori	2011	3	Biliary tree	N3	45months-48months-90months
Murakami	2011	17	Biliary tree	N3	24% 5year survival
Liu	2013	6	Gallbladder	N2	16,6% à 5ans
Present series	2020	8	Gallbladder	N2+N3	16,3%

Table 5: Long survival for patient with infiltrative node beyond hepatic pedicle.

Conclusion

Extensive lymphadenectomy during radical surgery of gallbladder cancer is justified by the 3 and 5-year survival in selected patients. The selection criteria are no major patient organic disease and the possibility of a R0 resection. Several publications are in line with the realization of extensive lymphadenectomy seen the results achieved in long-term survival and some single lymph node recurrence after radical surgery without lymphadenectomy beyond the hepatic pedicle. The future will show to allow if the extensive lymphadenectomy with the possible importance lymph node extirpation provides help directly to the remote survival but also the choice of adjuvant therapy that considered in practice in coming years.

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