

Locally Advanced Gallbladder Cancer, New Strategies Offering Hope

Hector-Mauricio Almau^{1*}, Plinio Fernández² and Juan Larrañaga¹

¹Department of Surgery, Upper Digestive Tract and Hepato-Pancreatic-Biliary HPB Unit, Rancagua Regional Hospital, Chile

²Department of Medical Oncology, Rancagua Regional Hospital, Chile

***Corresponding Author:** Hector-Mauricio Almau, Department of Surgery, Upper Digestive Tract and Hepato-Pancreatic-Biliary HPB Unit, Rancagua Regional Hospital, Alameda, Chile.

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Abstract

The gallbladder cancer is a very aggressive disease with usually poor long term survival especially in locally advanced stages, with adequate patient selection aggressive surgery can be offered with up to 25% 5-year survival rates. The relatively new outcomes with neoadjuvant therapy followed by surgery make this option more reliable with astonishing results from some centers; therefore new protocols should be addressed in order to gain better results.

Keywords: Gallbladder Cancer; Locally Advanced Gallbladder Cancer; Neoadjuvant Therapy

Introduction

The gallbladder cancer (GBC) is a very aggressive entity, worldwide it is an uncommon cancer (2/100,000 hab), but there are some countries and regions with a high incidence and mortality, being high in Latin America, Asia and the north of India. In Chile it represents the second cause of death in women, especially between Mapuche Indians of Chile [1].

Due to the lack of symptoms most of the time the gallbladder cancers are diagnosed in an advanced stage, with a poor prognosis because of metastatic or inoperable disease, the other form of diagnosis is as an incidental finding in the biopsy after cholecystectomy [1].

It is understood that a locally advanced gallbladder cancer comprises a T3, tumor perforated serosa or directly invades the liver and/or one of the other adjacent organs and structures such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts; or a T4, tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures. These situations could be with or without lymph node involvement, comprising the stages III-A, III-B, IV-A, and IV-B (without M1). AJCC 8th edition [2].

Surgical outcomes closely correlate with the extent of tumor invasion, suggesting that survival after gallbladder cancer resection is stage-dependent, just a R0 surgical approach can offer a curative option or a disease control procedure. In stage IV GBC 5-year survival ranges between 0 to 20% [3].

The clinical presentation can preclude an advanced disease, such as: jaundice, weight loss, ascites, and abdominal pain. The presence of ascites is almost a confirmation of peritoneal carcinomatosis classifying the patient with metastatic disease. The presence of jaundice precludes a locally advanced cancer due to bile duct infiltration or lymph node metastasis with bile duct compression, and it is frequently associated in gallbladder neck and cystic duct cancer, most of the time jaundice is considered an ominous sign but some groups of patients may benefit from an aggressive surgical approach [3-5].

Outcomes in surgically treated patient for locally advanced gallbladder cancer

The eastern and western approaches are quite different, almost 30 years ago it was described the hepatopancreatoduodenectomy in Japan by Takasaky to treat locally advanced and metastatic gallbladder cancer, besides his results denote the aggressive surgical intention to treat the disease, now this procedure can be indicated only in selected cholangiocarcinomas but not in gallbladder cancers, because of the poor long-term prognosis associated with a high mortality and morbidity rate, 5-year survival ranges from 0% to 25% [3,6].

The Japanese results in locally advanced GBC can be seen in the paper of Chijiwa K., et al. 2007, exposing their outcomes of radical surgery in stage IV GBC in a period of 14 years, they enrolled 90 patients with GBC from those 37 comprise with stage IV who were operated, and they added 41 patients with stage IV not treated surgically in order to compare (TNM system of Japanese Society of Biliary Surgery) [7].

For patients stage IVa (T2N3, T3N2, T4N0,1) had the better survival rate when compared with stage IVb (T3N3, T4N2,3, liver, peritoneal and distant metastasis). But contrasting both stages with patients without surgical treatment, the surgical treatment showed better survival rate, no patient in the nonsurgical group lived after 20 months. Analyzing the presence or not of liver metastasis, patients submitted to surgery with liver metastasis had the same survival that patients not treated surgically and when they compared patients according just to the TN, excluding liver metastasis, peritoneal dissemination and distant metastasis, found that the worst prognosis were in the patients with N3 regardless the T factor, and the best survival rate were in patients with T4N0. These results show that distant nodal metastasis N3 (peripancreatic head except posterosuperior head, celiac, mesenteric and/or paraortic lymph node) it is an independent factor for survival as well as metastatic disease [7].

More recently Nasu Y., et al. 2016, reported their result on aggressive surgery for locally advanced GBC with obstructive jaundice, they analyzed 65 patients with T2, T3 and T4 the number of patients were 12, 18 and 35 respectively. Of the 65 patients 30 had N0 and 35 N1, so they were classified in stages II, IIIA, IIIB, IVA, IVB. The OS rates were at 1, 3, and 5 years 74, 39 and 29% respectively. The 5-year survival rates related to tumor invasion were 64, 17 and 26% for T2, T3 and T4 respectively. When the data were divided between patients with lymph node metastasis or not, it showed a 5-year survival of 39 and 15% for N0 and N1 respectively. As it was mentioned before jaundice is considered as an ominous sign, in this paper they analyzed and divided the patients with or without jaundice finding no difference between the groups, 5-year survival rates were 31 and 27% respectively [3].

The prognosis factors that significant impact on long term survival on univariate analysis were: Blood loss, portal vein infiltration, lymphovascular infiltration, liver metastasis, distant and regional lymph node metastasis and residual tumors. The multivariate analysis showed only liver metastasis and distant lymph node metastasis as a predictor of poor survival, both analyses excluded jaundice as a poor prognosis sign, and in patients with jaundice after excluding liver metastasis and distant lymph node showed an OS rate of 63% [3].

In 2015 it was published the Gallbladder cancer: expert consensus statement by Aloia T., et al. they recommend for the management of locally advanced GBC with adjacent organ involvement T3 or T4 saying "radical resection of locally advanced primary tumours should, therefore, be performed only in medically fit patients after multidisciplinary discussion. Although R0 resection for GBC is associated with longer survival, tumour biology and stage, rather than the extension of the resection, are the most important predictor of survival after surgery", the expert consensus opens the possibility to perform aggressive surgery in well selected patients warning about the benefit particularly in patients with jaundice [8].

In 2017 was published a paper with a multicenter database of the US Extrahepatic Biliary Malignancy Consortium (USEBMC) by Tran T., et al. analyzing the outcomes of patients with GBC and jaundice, the final cohort data analyzed 33 patients with jaundice and 218 patients without jaundice, the OS was worse in patients with jaundice, but when stratified by stages, stage III-A showed no differences, and with significant differences in stages III-B and IV, demonstrating that without lymph node involvement jaundice makes no difference on survival. In order to understand the value of surgery in patients with jaundice they observed that in the absence of lymphovascular invasion had better survival compared with lymph node metastasis (median 40.5 vs 13.8 months respectively; $P = 0.014$) and in patients with jaundice but with CA 19-9 below 50 U/ml showed better survival rates than patients with CA 19-9 above 50 U/ml (median 40.4 vs 12.1 months respectively; $P = 0.0034$, being those two elements independent prognostic factors for survival [5].

Kurahara H., et al. 2018, published an article about the indication of extrahepatic bile duct resection for gallbladder cancer, they divided the tumors anatomically into proximal type (gallbladder neck and cystic duct) and distal type (gallbladder body and fundus). The outcomes in association between clinicopathologic factors and tumor location demonstrated that proximal-type tumors showed lower R0 resection rates compared with distal-type tumors $P = 0.005$, and it was observed more lymph node metastasis (> 3 lymph nodes) and higher rates of perineural invasion in proximal types vs distal types ($P = 0.029$, $P = 0.012$ respectively). The extrahepatic bile duct resections had a positive impact on patients with proximal-type tumors with a 5-year survival rate of 46.4%, and reduced the rate of local and lymph node recurrence [9].

Surgical strategy for locally advanced gallbladder cancer

The appropriate patient selection is crucial especially in situation of locally advanced GBC, Nasu Y, *et al.* published their department policy for treating GBC, where they took into consideration key prognostic factors such as peritoneal dissemination, liver metastasis and para-aortic lymph node metastasis to avoid unnecessary surgeries, they do not consider jaundice as a barrier itself, but if the patient can reach bilirubin levels below 2 mg/dl after biliary drainage they can pursue for an eventual surgery [3]. The data published by Tran T, *et al.* founding that a cutoff point below 50 U/mL of CA 19-9 and the absence of lymphovascular invasion as a good predictor of survival, this could be part of the preoperative evaluation in order to treatment decision making [5]. In 2017 Kumar Mishra P, *et al.* founded that curative resection were done significantly more in patients without jaundice $P = 0.001$, the negative predictor factors were: abdominal pain, anorexia, significant weight loss, gastric outlet obstruction, hepatomegaly, abdominal lump and presence of jaundice, but when it was compared the survival rate between patients with jaundice and locally advanced tumors without jaundice, there were no statistical difference, suggesting that other factors may influence the long term survival, those factors were TNM stage, the N status and the infiltration of adjacent organ $P < 0.001$ [10].

So far it can be said that jaundice is a warning sign for patients with GBC, an individual patient evaluation has to be done considering the long term survival predictor factors in order to move forward for surgery.

Neoadjuvant therapy for gallbladder cancer

As a consequence of the poor prognosis in locally advanced gallbladder cancer, neoadjuvant therapies have been proposed, the expert consensus statement 2015 suggests that gemcitabine and cisplatin regimen should be used as the best chemotherapy scheme, beside the lack of data from randomized control trials [8].

In 2016 was published by Engineer R, *et al.* at the Tata Memorial Hospital, Mumbai India, the first prospective study evaluating the outcomes of neoadjuvant chemoradiation followed by surgery for locally advanced GBC, the results were astonishing. Patients were recruited from October 2008 to June 2013, a total of 41 patients with locally advanced GBC, proved by a positive FNA cytology for adenocarcinoma were included, after patient selection 25 patients completed neoadjuvant chemoradiation (57 Gy with gemcitabine 300 mg/m²/week), 5 were discharged for metastasis disease and 2 refused surgery, 18 patients enrolled to surgery, from those, they founded peritoneal metastasis in 4, remaining 14 patients where they could perform R0 resection. When it was evaluated the pathological response by a scale of tumor regression grade, founded: 4 patients (14.3%) with 0/3 grade, which means no viable cancer cells, 3 patients (10.7%) 1/3 grade, which means single cells or small groups of cancer cells and 3 patients (10.7%) with 2/3 grade, which means residual cancer outgrown by fibrosis. These results demonstrated that 10 of 14 patients had pathological response and half of the patients had significant pathological response. The 5 year survival rate was 47% for patients undergoing R0 resection [11].

Creasy J, *et al.* 2017 from Memorial Sloan Kettering Cancer Center, published their retrospective data of patients with locally advanced or lymph node positive GBC who received chemotherapy previous to surgery, the data were collected from 1992 to 2015, all the patients were administered gemcitabine based chemotherapy and 57% received gemcitabine plus cisplatin. 23% of patients had progression during treatment, for patients who could reach surgery the OS was 51 months versus 11 months for those with unresectable disease [12].

Chaudhari V, *et al.* 2018 from Tata Memorial Hospital, Mumbai India, demonstrated their results with neoadjuvant chemotherapy in locally advanced/borderline resectable GBC, in order to classify the patients they used the THM criteria, taken in consideration T3 or T4 tumors: contiguous liver involvement > 2cm, involvement of bile duct causing obstructive jaundice, radiological or endoscopic involvement of stomach, duodenum, hepatic flexure of colon or small intestine. Lymph node infiltration on stage N1: radiological suspicion of lymph node involvement at stages 8, 12, 13, size >1cm in short axis, round shape and heterogeneous enhancement on CT/PET scan. Vascular invasion: impingement/involvement (< 180-degree angle) of one or more of the following blood vessels, common hepatic artery, right and left hepatic artery, main portal vein and right and left branches. For incidental GBC: residual/recurrent mass in GB fossa, N1 nodes, involvement of bile duct.

They used essentially two types of chemotherapy regimens that comprised GEMCIS (gemcitabine 1000 mg/m² as a 30-minute infusion on dayⁿ, 8 and cisplatin 25 mg/m² on day 2 over 2 h every 14 days) or GEMOX (gemcitabine 1000 mg/m² on dayⁿ as a 100-minute infusion and oxaliplatin 100 mg/m² on day 2 over 2h every 14 days). The analysis of response was made with CT-PET scan after 3 or 4 cycles of chemotherapy using a RECIST criteria. Patients who fit for surgery complete 6 months as a perioperative therapy. The study included 160 patients, 34 patients debuted with jaundice requiring biliary drainage previous to neoadjuvant treatment. 67 patients

(42%) could not be operated, the main reason was disease progression at 27% of cases. The survival analysis showed an OS and EFS of 13 months and 8 months respectively, but when it was analyzed the patients with complete response/complete metabolic response and partial response had much better survival with OS of 49 months and 25 months respectively [13].

Conclusions

These new evidence demonstrate the important role that play neoadjuvant regimens on long term survival rates, achieving 47% 5 years survival rate, 51 months or 49 months survival against 25% 5 years survival rate in the best up front surgery series [7,11-13].

Also it is significant to differentiate patient with more favorable tumor biology, those who response to neoadjuvant regimes from those who do not, in order to offer radical surgical procedure in patients with better chance to survive for long term period.

Conflicts of Interest

The authors do not have any conflict of interest.

Bibliography

1. Ivan Roa, *et al.* "Gallbladder cancer in Chile: what have we learned?" *Current Opinion Gastroenterology* 31.3 (2015): 269-275.
2. Mahul B Amin, *et al.* "AJCC Cancer Staging Manual 8th edition". Springer 24 (2017): 303-308.
3. Yuya Nasu, *et al.* "Aggressive surgery for locally advanced gallbladder cancer with obstructive jaundice: result of a prospective study". *Digestive Surgery* 33 (2016): 213-219.
4. Vinay K Kapoor. "Advanced gallbladder cancer: Indian middle path". *Journal of Hepato-Biliary-Pancreatic Surgery* 14.4 (2007): 366-373.
5. Thuy B Tran, *et al.* "Gallbladder cancer presenting with jaundice: Uniformly fatal or still potentially curable?" *Journal of Gastrointestinal Surgery* 21.8 (2017): 1245-1253.
6. Tokoki Ebata, *et al.* "Review of hepatopancreatoduodenectomy for biliary cancer: an extended radical approach of Japanese origin". *Journal of Hepato-Biliary-Pancreatic Sciences* 21.8 (2014): 550-555.
7. Kazuo Chijiwa, *et al.* "Outcome of radical surgery for stage IV gallbladder carcinoma". *Journal of Hepato-Biliary-Pancreatic Surgery* 14 (2007): 345-350.
8. Thomas A Aloia, *et al.* "Gallbladder Cancer: expert consensus statement". *HPB* 17.8 (2015): 681-690.
9. Hiroshi Kumura, *et al.* "Indication of extrahepatic bile duct resection for gallbladder cancer". *Langenbeck's Archives of Surgery* 403.1 (2018): 45-51.
10. Pramod Kumar Mishra, *et al.* "Predictors of curative resection and long term survival of gallbladder cancer – a retrospective analysis". *The American Journal of Surgery* 214.2 (2017): 278-286.
11. Reena Engineer, *et al.* "Neoadjuvant Chemoradiation follow by surgery for locally advanced gallbladder cancers: A new paradigm". *Annals of Surgical Oncology* 23.9 (2016): 3009-3015.
12. John M Creasy, *et al.* "Systemic chemotherapy combined with resection for locally advanced gallbladder carcinoma: Surgical and survival outcomes". *Journal of the American College of Surgeons* 224.5 (2017): 906-916.
13. Vikram A Chaudhari, *et al.* "Outcome of neoadjuvant chemotherapy in locally advance/borderline resectable gallbladder cancer: the need to define indications". *HPB* (2018).

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