

# Case Report

## Aggressive Surgical Approach to Treat Gallbladder Cancer: Is it Worth it?

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### Abstract

The treatment of locally advanced gallbladder cancer has shifted in the past years, leading to a more aggressive surgical approach. We report a case of a 61-year-old woman diagnosed as having a locally advanced gallbladder cancer who was submitted to an aggressive surgical procedure in order to achieve complete resection (R0 resection). At laparotomy, a huge gallbladder tumor was seen with gross invasion of the transverse colon, distal part of stomach, pancreatic head, duodenum and liver. No distant metastases were seen. Surgical approach consisted in an en bloc tumor resection, including pancreatoduodenectomy, distal gastrectomy, right colectomy, hepatic resection (segments IVb, V and VI) and radical lymphadenectomy. The final pathology report revealed adenocarcinoma of the gallbladder with invasion to the nearby organs (liver, stomach, duodenum, head of the pancreas and colon) and no lymph nodes metastases (T4N0M0). All margins were free (R0 resection). Adjuvant chemotherapy was given (cisplatin and gemcitabine). The patient had been well (asymptomatic and with good quality of life) for 10 months when developed liver metastases not amenable to resection. The patient is being treated with palliative chemotherapy (gemcitabine and oxaliplatin). A marked improvement in outcome (survival and quality of life) of patients with gallbladder cancer has been achieved over the past years, primarily due to a shift towards more aggressive surgery. Therefore, this approach might be beneficial for selected patients with locally advanced gallbladder cancer

**Keywords:** Gallbladder Neoplasms; Surgery;

### Introduction

Gallbladder cancer (GBC) is an aggressive malignancy that occurs mostly in elderly patients, corresponding to 75% of the cases in those aged more than 65 years. It is the fifth most common gastrointestinal malignancy, two to three times more common in women than men, in part because of the higher incidence of gallstones in this sex. Besides the exceptional cases detected incidentally during cholecystectomy, which are usually early stage, the prognosis for most patients is poor.<sup>1</sup> Studies from the West have reported 5-year survival rates of only 5% to 38%.<sup>2-4</sup> Unfortunately, many of these tumors are unresectable at presentation,

and most could be managed nonoperatively. Since the only effective treatment for this cancer remains operative resection, efforts should be made to increase resectability and improve survival by expanding the operative procedure using more extensive hepatic resection, pancreatoduodenectomy, and extended lymphadenectomy. Recently, an aggressive surgical approach for patients with localized gallbladder cancer has been proposed based on encouraging results.<sup>5-7</sup>

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## Case Report

A 61-year-old woman presented with right upper quadrant abdominal pain spanning a two month period with neither jaundice nor weight loss. The patient had diabetes and hypertension with irregular treatment and no familiar history of biliary tree pathology. Physical examination showed a good performance status and a palpable mass over the right upper abdominal quadrant. A sonographic study revealed a heterogeneous mass surrounding the gallbladder with an irregular wall associated with several gallstones. MRI of the abdomen showed a mass over the gallbladder, extending to the liver (Figure 1). CA 19-9: 0.6ng/mL, CEA: 206ng/mL. After

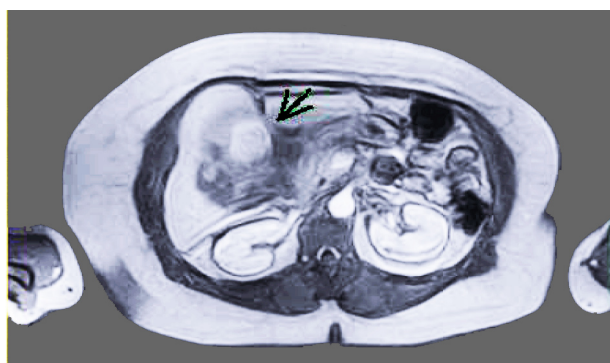


Figure 1-Preoperative image showing a mass over gallbladder topography

staging exams, the patient underwent a surgical procedure which revealed a huge gallbladder mass (Figure 2) with gross invasion of the transverse colon, distal part of stomach, pancreatic head, duodenum and liver. The surgical approach consisted in an en bloc tumor resection, including pancreatoduodenectomy, distal gastrectomy, right colectomy, hepatic en bloc resection (segments IVb,V and VI) and radical lymphadenectomy (Figure 3 and Figure 4).

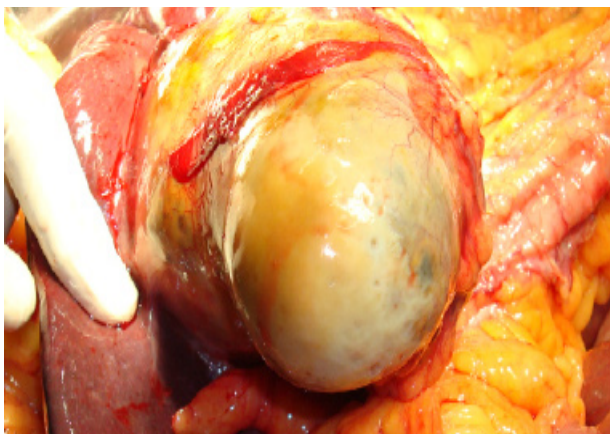


Figure 2- En bloc liver resection (segments IVb,V and VI)

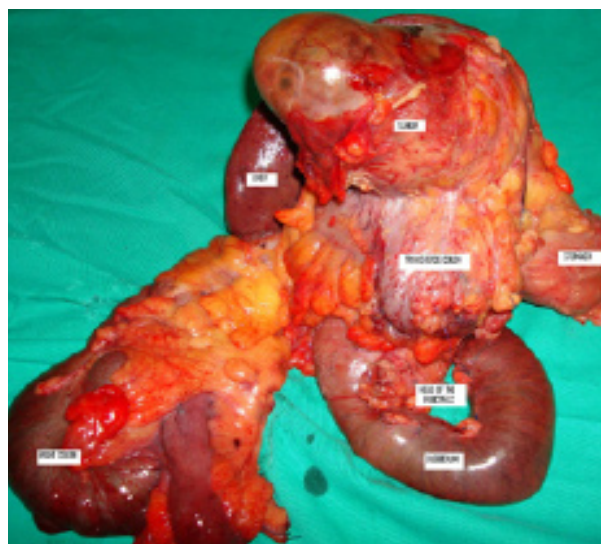


Figure 3- Surgical specimen consisting in an en bloc tumor resection ( pancreatoduodenectomy, distal gastrectomy, right colectomy, hepatic resection)

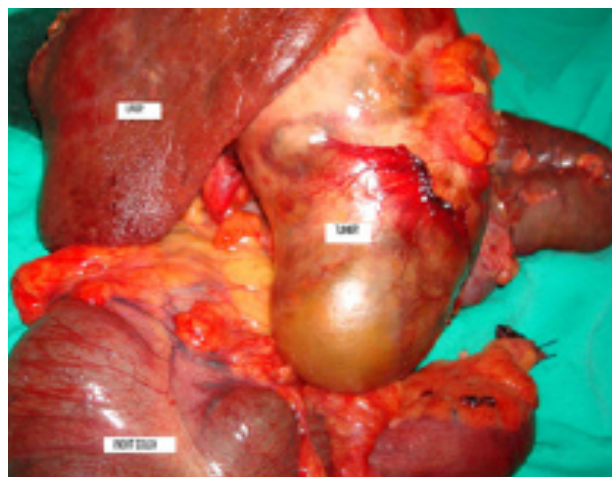


Figure 4 -Intraoperative aspect of the gallbladder tumor invading the surrounding organs

The final pathology report revealed adenocarcinoma of the gallbladder with invasion to the nearby organs (liver, stomach, duodenum, head of the pancreas and colon) and no lymph node metastases within twenty isolated lymph nodes (T4N0M0). All margins were free (R0 resection). The patient was discharged after 20 days.

Adjuvant chemotherapy was given (6 cycles of cisplatin and gemcitabine). CEA level had decreased to 10 ng/ml after surgery. The patient remained asymptomatic during 10 months of the follow-up, when presented with abdominal pain and periumbilical mass and increasing CEA level. On physical examination, it was observed a periumbilical mass suggestive of disease recurrence. CT scan showed liver metastases and palliative chemotherapy was initiated (gemcitabine and oxaliplatin).

## Discussion

Gallbladder cancer spreads by four routes: direct invasion to adjacent organs, via lymphatic channels, hematogenous spread and peritoneal dissemination. The risk of peritoneal and distant nodal metastasis, in addition to direct invasions, is related to the depth of penetration through the gallbladder wall.<sup>8-9</sup> Furthermore, because of its anatomical location, in addition to the liver, this cancer easily invades the colon, duodenum, and vessels in the hepatoduodenal ligament. For this reason, invasion of these adjacent organs is frequently seen in the advanced stage of disease.

It is clear that the surgical treatment of T1 and T2 lesions has been considered the standard of care, leading to cure and long term survival. On the other hand, the surgical treatment of locally advanced tumors (T3 and T4 lesions) has been seen with skepticism due to poor prognosis reported in some series decades ago<sup>4-5</sup>. However, this thinking has changed in the last years due to good outcomes reported by Dixon et al.<sup>2</sup>, even in locally advanced disease. These authors showed that the changing of the surgical approach was responsible for the improvement outcome in T3 and T4 tumors, with the median 5-year survival rising from 7% to 35% after aggressive treatment, with considerably low mortality and morbidity. Indeed, not only T stage, but also N stage, is considered a prognostic factor. In patients estimated preoperatively or found intraoperatively to have N1 lymph node metastases, according to the 2002 AJCC/UICC classification, even without adjacent organ invasion, radical surgery may not help in achieving a good outcome. The N stage is reported to be related to the T stage. In Shimada's report,<sup>8,10</sup> 11 out of 16 T3 and T4 patients (68.8%) had greater than N2 lymphatic spread, and, in Tsukada's series,<sup>9</sup> 24 out of 34 T3 and T4 patients (70.6%) had a stage greater than N2 (according to the Japanese and 1997 AJCC/UICC). Thus, when T3 or T4 patients are selected on the basis of the N stage, about 30–60% of patients may be suitable for radical surgery. The most recent classification used for GBC, the 2002 AJCC/UICC, which proposes N0 as negative lymph node metastasis and N1 as positive, isn't yet fully accepted, opposing to the use of 1997 classification that states N1 as metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes and N2 as metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes, that still remains, for many authors, the chosen one for gallbladder cancer.

There have been several studies that have examined prognostic factors in gallbladder cancer.<sup>4,10-11</sup> Fong et al.<sup>10</sup>

presented a detailed analysis of one of the largest single-institute experiences, and, in their series, the N stage was reported to be one of the prognostic factors by multiple regression analysis (N stage:  $P < 0.0004$ ; T stage  $P < 0.003$ ; Nevin stage:  $P < 0.0001$ ). The surgical outcome for node positive gallbladder cancers varies between different reports. Although many Western studies have reported few long-term survivors in patients with documented nodal metastasis<sup>12-13</sup>, data from Japanese centers indicate the possibility of long-term survival.<sup>14-16</sup> Shimada et al.<sup>8</sup> reported a 5-year survival rate of 60% for patients with metastasis to N1 nodes after extended cholecystectomy, whereas Shirai et al.<sup>15</sup> reported a 5-year survival rate of 45% for patients with positive regional nodes.

Lesions that are initially staged as T2 or T3 are treated with liver resection, either a segment IVb/V resection, right hemihepatectomy or an extended right hepatectomy. The decision regarding the type of liver resection is based somewhat on the anatomic location of the tumor. Lesions located predominantly in the fundus can be treated with a segment IVb/V resection. Those located in the Hartmann pouch, the gallbladder neck, or extending into the triangle of Calot (i.e., those close to the hilar plate and biliary confluence) require an extended liver resection to ensure negative margins. This requires resection of the extra hepatic/pancreatic biliary tree, including the horizontal course of the left hepatic duct over to the umbilical fissure. In these cases, an extended right hepatectomy is generally performed with reconstruction to the left hepatic duct at the base of the umbilical fissure. All T4 lesions are likewise treated with extended hepatectomy. Segment IVb/V resections are limited to those patients with T3 or lower fundal lesions and in those patients in which there is clearly a negative margin towards the right pedicle/plate. Extended hepatectomy is performed in all patients with T4 lesions or any lesion in which a negative or close margin is a concern. All jaundiced patients, patients with bulky nodal disease along the hepatoduodenal ligament, and any other patient with a positive cystic duct margin undergo a biliary resection. Other contiguous organ involvement is resected en bloc, as presented in our case report. Patients with obvious N2 lymph node metastasis, extended radical resection may be of no use. A randomized trial comparing extended versus limited surgical resection would be the ideal manner to test this concept, but this cannot be performed because of the paucity of cases, as well as the lack of therapeutic equipoise, given the current evidence.<sup>17-32</sup>

Multivariate examination accounting for the time period in which treatment occurred reveals that the most

important factor determining long term survival is whether the patient underwent an R0 surgical resection.<sup>2</sup> We could learn with this case report that the aggressive surgical approach was really beneficial for the patient, because not only improved survival but also quality of life. Despite the recurrence ten months after surgery, the patient still had a good quality of life, being able to do all her routine activities. Another issue to be commented was the unusual finding of the high CEA level. Despite being already published,<sup>33-34</sup> this finding may difficult the GBC diagnosis.

In summary, a marked improvement in outcome (survival and quality of life) of patients with gallbladder cancer has been achieved over the past years, primarily due to a shift towards more aggressive surgery; however, even in the most recent time period, a maximal 5-year survival rate of only 35% has been achieved,<sup>2</sup> confirming gallbladder cancer as an extremely lethal disease which stills challenges the surgeon.

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