EDITORIAL

Gallbladder Carcinoma Surgical Therapy. An Overview

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Introduction

Carcinoma of the gallbladder is the most frequent tumor of the extrahepatic biliary tract, and the fourth commonest upper gastrointestinal malignancy. Of the histologic types, adenocarcinoma is the most frequent (80%) (1,2).

Gallbladder cancer probably has a multifactorial etiology. More than 80% of patients diagnosed with gallbladder cancer have gallstones. Karyotipic abnormalities, such as mutation of the tumor suppressor gene p53, which is located on the short arm of chromosome 17, are common in gallbladder cancer. Anomalous junction of the cystic duct and the common bile duct, pancreatobiliary maljunction, cystic disorders of the biliary tree or gallbladder polypoid lesions have been observed frequently in patients with gallbladder cancer (3,4).

Prognosis

Despite advances in preoperative diagnostic and surgical techniques, carcinoma of the gallbladder is still associated with a poor prognosis because it generally presents late with a short history of non-specific abdominal symptoms, and a direct extension to adjacent vital organs frequently occurs at presentation (1,5).

Some recent reports suggest an improved prognosis in a minority of patients with early tumors that are diagnosed incidentally on pathological examination of cholecystectomy specimens. This is the case of "incidental" or fortuitous gallbladder carcinoma (5-7).

Pathologic staging

Neoplastic cells may diffuse by a) perineural invasion (adverse prognostic factor) (8), b) venous invasion (gallbladder veins drain directly into the liver bed and are tributaries of the middle hepatic vein), c) lymphatic invasion (9).

Loco-regional lymph nodes are disposed along the main arteries and include the cystic duct, pericholedochal, hilar (hepatoduodenal ligament, inferior caval vein), peri-pancreatic (head), periduodenal, periportal, coeliac, superior mesenteric and para-aortic lymphatic chains (10,11).

The TNM classification and stage grouping criteria are useful to predict survival and decide therapy (Tables I-IV) (12).

Table I Pathologic staging (pTNM) of gallbladder carcinoma. Primary tumor (pT)

pTis	carcinoma in situ
pT1	tumor invades lamina propria or muscle layer
	pT1a tumor invades lamina propria
	pT1b tumor invades muscle layer
pT2	tumor invades perimuscolar connective tissue; no extension beyond serosa or into liver
pT3	tumor perforates serosa (visceral peritoneum) and/or directly invades the liver and/or other adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extrahepatic bile ducts
pT4	tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Table II Pathologic staging (pTNM) of gallbladder carcinoma. Regional lymph nodes (pN)

pN0	no regional lymph node metastasis
pN1	regional lymph node metastasis

Table III Pathologic staging (pTNM) of gallbladder carcinoma. Distant metastases (pM)

pM0	no distant metastasis
pM1	distant metastasis

Gallbladder cancer can be diagnosed 1) before operation, 2) at the time of cholecystectomy, or 3) on pathological examination of cholecystectomy specimen.

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Table IV Gallbladder carcinoma stage groupings

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	N0-1	M0
Stage IV	any T	any N	M1

Surgical approach

If gallbladder carcinoma is diagnosed *preoperatively* a careful staging is needed by imaging techniques (US, cholangio-MR, angio-TC, MRI, PET, PTC, ERCP with common bile duct brushing), and laparoscopy. A percutaneous biopsy must be avoided because of the real danger of spreading. Peritoneal spreading is an absolute contraindication to surgery (1).

For stage 0 (Tis) and early stage I (T1a) patients a cholecystectomy alone is associated with excellent survival and no further treatment is required. It is essential that the cystic duct margin is not involved with tumor (6,7).

Lymph node metastases are common in the late stage I. T1b patients need a cholecystectomy with bed wedge resection (2 cm) and lymphadenectomy with skeletonization of the hepatic pedicle. For T2 patients a cholecystectomy with hepatic bisegmentectomy IVb-V and extended lymphadenectomy (hepatic pedicle, peripancreatic, coeliac) is recommended. When involved the common bile duct must be resected (13). Operative mortality (5%) and operative morbidity (30%) are not neglectable (14,15).

For stage II patients with liver involvement (T3) or lymph node metastases (N1) and for stage III patients with adjacent organ infiltration (T4) a wide ("en bloc") radical resection is suitable only for selected cases. Hepatectomy, pancreatoduodenectomy, and para-aortic lymphadenectomy have been attempted but the operative mortality (20%) is important if compared to the 3-year survival (19%) and a real curative benefit is controversial (16-21).

If gallbladder cancer is diagnosed *intraoperatively* a laparoscopic occurrence must be distinguished from a laparotomic one. During a laparoscopic approach the prognosis is worse on account of the risk of peritoneal dissemination (16%) and the high incidence of port site recurrence (17%). The conversion to an open technique is mandatory with excision of port sites and tumor exeresis (radical, palliative) according to TNM (22,23).

Tumor exeresis (radical, palliative) is performed according to TNM also during a laparotomic approach.

If gallbladder carcinoma is diagnosed *postoperatively* a surgical abstention is advisable for "incidental" gallbladder carcinoma (Tis, T1a) (0.35-2%). A re-staging and a re-resection according to TNM are advisable for late stage I (T1b, T2) (5-7).

Radical re-resection may be considered for selected patients with T3 or T4 tumors but variable results have been reported after aggressive surgery (16-21).

Patients with unresectable gallbladder cancer may undergo palliative surgical treatment (cholecystectomy; cholecystectomy + cholangiojejunostomy; segment III by-pass) (1) or medical treatment: endoscopic or percutaneous biliary stenting; chemotherapy (24,25) with fluorouracil or mitomicin C or epirubicin or gemcitabine (median survival rate 8 months); radiotherapy.

New chemotherapeutic agents are needed for patients with residual tumors after surgery. Neoadjuvant therapy may increase the respectability rate of locally advanced tumors (3).

Conclusion

Patients diagnosed incidentally on pathological examination of cholecystectomy specimens have an improved survival and should be considered for further radical re-resection. Their prognosis is significantly better compared to the prognosis of patients whose gallbladder cancer has been diagnosed preoperatively or at the time of cholecystectomy (1).

Patients undergoing radical resection and patients in whom a cholecystectomy alone was considered curative ("incidental" gallbladder carcinoma) have a better outcome (5-year survival 35-38%) than those who did not undergo curative surgery (median survival 5 months) (26).

For more radical operations including "en bloc" resections and pancreatoduodenectomy a real survival benefit is controversial.

Lymph node involvement (LNI) and bile duct infiltration (BDI) are important prognostic factors. In fact, the 3-year survival rate is 65.6% for LNI (-) and BDI (-) vs 35.3% for LNI (+) and BDI (-) vs 14.3% for LNI (-) and BDI (+) vs 5.9% for LNI (+) and BDI (+) (27).

Lymph nodes must be carefully investigated by histology, immunohistochemistry, and nonmorphological (molecular) techniques to exclude also *micrometastases*, that cause tumor recurrence (28).

The postoperative prognosis is very much dependant on the first surgical approach which must have been chosen correctly.

The best surgical therapy of gallbladder cancer is its *prevention.* Therefore, patients with symptomatic gallstones, anomalous biliary or pancreatobiliary junction, cystic disorders of the biliary tree or gallbladder polypoid lesions greater than 1 cm must undergo cholecystectomy (3,4).

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