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ScienceDirect

EJSO 40 (2014) 1008–1015

EJSO the Journal of Cancer Surgery

www.ejso.com

# Locally advanced gallbladder cancer: Which patients benefit from resection?

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Accepted 19 October 2013
Available online 5 November 2013

**Abstract**

*Objectives*: Patients with T3–4 gallbladder cancers (GBCs) often require extended surgical procedures, and up to 30% of patients have N2 metastases. This study investigated which patients with T3–4 GBC benefit from resection.
*Methods*: Consecutive patients ($n = 78$) with T3–4 GBC who underwent resection between 1990 and 2011 were analysed (38 before 2003, 40 in 2003–2011). Forty patients required common bile duct (CBD) resection, 10 pancreatoduodenectomy, 4 right colectomy and 2 gastric resection. Fifty-two (67%) patients had LN metastases, including 22 with N2 metastases.
*Results*: The in-hospital mortality rate was 8%, 11% before 2003 vs. 5% in 2003–2011. The morbidity rate (47%) remained stable during the study. Undergoing liver and pancreatic resection did not increase severe morbidity (0%) or mortality (10%). Sixty-seven (86%) patients had R0 resection. The 5-year survival rate was 17% (median follow-up, 65 months). Survival improved after 2002 (26% vs. 9%, $p = 0.04$). R1 patients had poor 3-year survival (0% vs. 32%, $p = 0.001$). N+ patients also had low survival (5-year survival, 10% vs. 32% in N0, $p = 0.019$), but N1 and N2 patients had similar outcomes. CBD resection and major hepatectomy did not worsen prognosis. Patients requiring pancreatoduodenectomy, gastric or colonic resection had 0% 3-year survival ($p = 0.036$ in multivariate analysis).
*Conclusions*: Resection of T3–4 GBC is worthwhile only if R0 surgery is achievable. Outcomes improved in most recent years. N2 metastases should not preclude surgery. Good results are possible even with CBD resection or major hepatectomy, while benefits from surgery are doubtful if pancreatoduodenectomy or other organ resection is needed.


*Keywords:* Gallbladder cancer resection; Pancreatoduodenectomy; Common bile duct resection; Survival; Liver surgery; Prognostic factors

## Introduction

Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide.[1] Complete surgery is the only curative therapy, whereas chemotherapy offers a limited contribution to survival.[1–4] Because it causes few symptoms, GBC is often diagnosed at an advanced stage and is resectable in only 15%–40% of patients.[1–3] Surgical outcome depends strongly on tumour stage: while excellent survival rates of up to 100% at 5 years have been reported for early stage disease (T1–2), overall survival rates range from 0% to 30% in locally advanced tumours (T3–4).[5–8]

To be completely resected, locally advanced GBCs often require extended surgical procedures, such as major hepatectomy, common bile duct (CBD) resection or pancreatoduodenectomy. In addition, lymph node (LN) metastases in the celiac and retropancreatic area are detected in up to 30% of patients.[8,9] The surgical indications in these patients are still being debated. A few series involving a limited number of patients, mainly in Asian centres, have reported conflicting results.[9–15]

During the last 20 years, we have adopted an aggressive surgical policy in patients affected by locally advanced GBC. Extended surgical procedures have been performed as long as complete resection was achievable. The present analysis reviewed the outcomes of this aggressive surgical approach, with particular attention to patients who required resection of other organs, e.g. CBD resection or pancreatoduodenectomy. The aim of the study was to identify which patients with locally advanced GBC benefit from resection.

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http://dx.doi.org/10.1016/j.ejso.2013.10.014

## Materials and methods

A total of 126 consecutive patients underwent resection for GBC at the Mauriziano Umberto I Hospital of Torino between January 1990 and December 2011. This study analysed the 78 (62%) patients with T3 or T4 GBC.

### *Patient management*

Preoperative staging routinely included carcinoembryonic antigen (CEA) and CA 19-9 value determination and thoraco-abdominal computed tomography (CT). Since 1998, magnetic resonance cholangio-pancreatography (MRCP) has been performed in all jaundiced patients or whenever CBD infiltration was suspected at CT. In recent years, contrast-enhanced magnetic resonance imaging and positron emission tomography CT were performed in case of uncertain diagnosis or suspected extra-hepatic disease, respectively.

Since 1998, CT-volumetry has been performed regularly in patients scheduled for major hepatectomy to estimate the future liver remnant (FLR) volume. The FLR was considered adequate if >25% of the total liver volume. In jaundiced patients, a higher cut-off of >30% was adopted. If the FLR was inadequate, preoperative portal vein embolization (PVE) was performed, and CT-volumetry was repeated 4 weeks later. Surgery was scheduled only if adequate FLR hypertrophy was observed. In jaundiced patients, preoperative biliary drainage was not performed on a routine basis. Its indications were cholangitis, malnutrition or the need for PVE (drainage of the FLR only).

### *Indications*

Surgery was performed whenever complete resection was achievable. Distant metastases, extensive infiltration of the hepatoduodenal ligament and interaorto-caval LN metastases were contraindications to surgery. The surgical indication was evaluated on a case-by-case basis when celiac or retropancreatic LN metastases were present. The indications for CBD resection were as follows: macroscopic CBD infiltration; LN metastases of the pedicle infiltrating the CBD; tumoral deposits along the hepatic pedicle; and neoplastic infiltration of the cystic duct stump in frozen section analysis. Pancreatoduodenectomy was performed in case of infiltration of the duodeno-pancreatic area by the GBC or by large retropancreatic LN metastases. Colonic or gastric resection was performed in case of macroscopic infiltration.

### *Surgical procedure*

The standard scheduled procedure for T3–4 GBC was segment 4b-5 resection (anatomic bisegmentectomy or wide wedge resection), en-bloc cholecystectomy and LN dissection. LN dissection was limited to the hepatic pedicle (D1) in the first part of the study (before 1998) and was extended to the retropancreatic and celiac area (D2) since 1998. Frozen section analysis of the cystic duct stump was performed regularly. In patients with a postoperative diagnosis of GBC after laparoscopic cholecystectomy, the trocar sites were systematically removed.

The surgical techniques used for liver resection, CBD resection and pancreatoduodenectomy have been described previously.[16,17] Since 2000, staging laparoscopy with laparoscopic ultrasonography always preceded laparotomy to exclude peritoneal carcinomatosis or liver metastases.

### *Adjuvant treatment and follow-up*

Postoperative chemotherapy was delivered according to patient performance status and pathological findings. All patients were followed-up every 3 months with a physical examination, CEA and CA 19-9 determinations and abdominal ultrasonography or thoraco-abdominal CT. No patient was lost during the follow-up period. This analysis includes follow-up to August 31, 2012.

### *Definitions*

Major hepatectomy was defined as resection of ≥3 Couinaud segments. Operative mortality was defined as death within 90 days after surgery or before discharge from the hospital. Morbidity included all postoperative complications and was classified according to the Clavien–Dindo classification.[18] Tumour TNM staging was reviewed according to the 7th edition of the AJCC manual.[19]

### *Statistical analysis*

Data were collected prospectively and analysed retrospectively. The series was divided into two periods in order to analyse outcome evolution during the study period. Continuous variables were compared between groups using the unpaired *t* test or the Mann–Whitney *U* test, as appropriate; categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to estimate overall survival (OS) and recurrence-free survival (RFS) probabilities, which were compared using the log-rank test. Patients with operative mortality or incomplete surgery (R2) were excluded from survival analysis. Multivariate analysis was performed using a Cox proportional hazard model to identify independent prognostic factors of OS and RFS after liver resection. Multivariate analysis was completed for factors with a $p$ value ≤0.10 in the univariate analysis. A $p$-value <0.05 was considered significant for all tests.

## Results

During the study period (1990–2011), 78 patients underwent surgery for T3–4 GBC, 38 before 2003 and 40