



## Prognostic heterogeneity of the seventh edition of UICC Stage III gallbladder carcinoma: Which patients benefit from surgical resection?

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### Abstract

**Background:** This study sought to evaluate the prognostic heterogeneity of Stage III (Union for International Cancer Control, seventh edition) gallbladder carcinoma.

**Methods:** Of 175 patients enrolled with gallbladder carcinoma who underwent radical resection, 22 were classified with Stage IIIA disease (T3N0M0) and 46 with Stage IIIB disease (T2N1M0 [n = 23] and T3N1M0 [n = 23]). The median number of retrieved lymph nodes per patient was 18.

**Results:** This staging system failed to stratify outcomes between Stages IIIA and IIIB; survival after resection was better for patients with Stage IIIB disease than for patients with Stage IIIA disease, with 5-year survival of 54.9% and 41.0%, respectively (p = 0.366). Multivariate analysis for patients with Stage III disease revealed independently better survival for patients with T2N1M0 than for patients with T3N0M0 (p = 0.016) or T3N1M0 (p = 0.001), with 5-year survival of 77.0%, 41.0%, and 31.0%, respectively. When N1 status was subdivided according to the number of positive nodes, 5-year survival in patients with T2M0 with 1–2 positive nodes, T2M0 with ≥3 positive nodes, T3M0 with 1–2 positive nodes, and T3M0 with ≥3 positive nodes was 83.3%, 50.0%, 45.8%, and 0%, respectively (p < 0.001).

**Conclusions:** The prognosis of T2N1M0 disease was better than that of T3N0/1M0 disease, suggesting that not all node-positive patients will have uniformly poor outcomes after resection of gallbladder carcinoma. T2M0 with 1–2 positive nodes leads to a favorable outcome after resection, whereas T3M0 with ≥3 positive nodes indicates a dismal prognosis.

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**Keywords:** Gallbladder neoplasms; Neoplasm staging; Lymphatic metastasis; Lymph node excision; Survival rate

### Introduction

Gallbladder carcinoma has a high propensity for metastasis to regional lymph nodes and lymph node metastasis is one of the most critical independent prognostic factors in this disease entity.<sup>1–3</sup> The tumor node metastasis (TNM) classification provided by the Union for International

Cancer Control (UICC) seventh edition classifies lymph nodes along the common bile duct, common hepatic artery, portal vein, and cystic duct as regional lymph nodes in gallbladder carcinoma; nodal disease beyond these regional nodes is considered as Stage IV, the same as locally advanced (T4) tumors and distant metastasis (M1).<sup>4</sup> Early local disease without regional metastasis (T1/2N0M0) is categorized as Stage I or II in this staging system; Stage III disease includes a heterogeneous group of patients.<sup>4</sup> Node-negative patients with advanced local disease (T3N0M0) are classified as Stage IIIA and regional node-positive patients with both early local disease (T1/2N1M0) and advanced local disease (T3N1M0) are

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classified as Stage IIIB,<sup>4</sup> even though the outcomes after resection for gallbladder carcinoma are known to be strongly associated with not only regional nodal metastasis but also the depth of tumor invasion through the gallbladder wall.<sup>5,6</sup>

T1 or T2 tumors are limited within the gallbladder wall, whereas T3 tumors perforate the serosa and/or directly invade the liver and/or one other adjacent organ or structure.<sup>4</sup> Some studies have reported uniformly poor outcomes in node-positive patients irrespective of T classification,<sup>2,7–9</sup> although the findings of other studies are not in agreement.<sup>10–13</sup> Thus, whether all regional node-positive patients with resectable (T1-3) gallbladder carcinoma have a similar poor prognosis require further investigation.

This study sought to evaluate the prognostic heterogeneity of Stage III gallbladder carcinoma. We also evaluated the lymphatic spread of T2/3N1M0 disease to clarify which node-positive patients would benefit from surgical resection with regional lymphadenectomy.

## Patients and methods

### Patients

A total of 188 consecutive patients with gallbladder carcinoma underwent radical resection (resection of both the primary tumor and regional lymph nodes) at Niigata University Medical and Dental Hospital between May 1982 and September 2012. Patients with cystic duct carcinoma were included in this study based on the UICC TNM staging system, seventh edition.<sup>4</sup> Of these 188 patients, 13 patients with invasive primary malignancy in other organs were excluded. The remaining 175 patients were enrolled in this retrospective study, including 66 men and 109 women with ages ranging from 39 to 85 (median, 68) years. This retrospective analysis was approved by the Institutional Ethics Committee. As this is a retrospective non-interventional study, the institutional review board waived the need for written informed consent from the patients.

### Operative procedures

The selection of the operative procedure for gallbladder carcinoma depended on the extent of tumor spread in individual patients (Table 1). In our department, an extended radical cholecystectomy was the most commonly performed procedure, consisting of cholecystectomy, wedge resection of the gallbladder fossa, resection of the extrahepatic bile duct, and lymph node dissection.<sup>5,14,15</sup> Wedge resection of the gallbladder fossa, bile duct resection, or both procedures were omitted in some patients with early-stage disease, advanced age, or comorbid disease.<sup>15</sup> More extensive operations, such as major hepatectomy, pancreaticoduodenectomy, and combined major hepatectomy and pancreaticoduodenectomy, were often performed

Table 1  
Operative procedures in 175 patients with gallbladder carcinoma.

Procedure	No. of patients
Extended cholecystectomy (n = 108)	
C + WR + BD	57
C + WR	24
C <sup>a</sup> + BD	15
C <sup>a</sup>	12
More extensive resection (n = 67)	
C + H + BD	37
C + WR + PD	15
C + H + PD	10
C <sup>a</sup> + PD	5

C, cholecystectomy; WR, wedge resection of the gallbladder fossa; BD, resection of the extrahepatic bile duct; H, major hepatectomy defined as removal of two sections or more; PD, Whipple, pylorus-preserving, or subtotal stomach-preserving pancreaticoduodenectomy.

<sup>a</sup> Cholecystectomy with full-thickness dissection.

in patients with late-stage disease.<sup>16,17</sup> In this series, 29 patients underwent combined resection of involved organs, including the transverse colon (n = 13), portal vein (n = 12), duodenum (n = 8), stomach (n = 2), and inferior vena cava (n = 2). Among the total 175 patients, 29 underwent radical resection as a second procedure after prior simple cholecystectomy for presumed benign disease.

In this series, limited distant metastasis was resected along with the primary tumor in 38 patients, including 21 patients with distant nodal disease, 12 with hepatic metastasis, 3 with distant nodal disease and hepatic metastasis, 1 with distant nodal disease and adjacent peritoneal seeding, and 1 with hepatic metastasis and adjacent peritoneal seeding.

### Extent of lymph node dissection

In our department, the cystic duct, pericholedochal, posterior superior pancreaticoduodenal, retroportal, and common and proper hepatic artery lymph node groups were dissected en bloc in most patients with suspected  $\geq$ T2 advanced gallbladder carcinoma.<sup>15–17</sup> Thus, in the present study, the posterior superior pancreaticoduodenal lymph nodes were treated as regional lymph nodes according to the Japanese TNM staging system.<sup>18</sup> In some patients with early-stage disease, advanced age, or comorbid disease, a less extensive lymphadenectomy procedure was selected at the discretion of the individual surgeons. In patients undergoing pancreaticoduodenectomy, the right portion of the superior mesenteric node group was also dissected together with the above mentioned lymph node groups. In this series, 99 patients with suspected metastasis to the regional lymph nodes also underwent dissection or sampling of the paraaortic nodes.<sup>15–17</sup>

### Pathological examination

The pathological findings were described according to the UICC TNM staging system, seventh edition.<sup>4</sup> The

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