
Residual Disease Predicts Outcomes after Definitive Resection for Incidental Gallbladder Cancer



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- BACKGROUND:** Residual disease (RD) at definitive resection of incidental gallbladder cancer (IGBCA) influences outcome, but its clinical relevance with respect to anatomic site is incompletely characterized.
- STUDY DESIGN:** Consecutive patients with IGBCA undergoing re-exploration from 1998 to 2009 were identified; those submitted to a complete resection were analyzed. Demographics and tumor- and treatment-related variables were correlated with RD and survival. Cancer-specific survival was stratified by site of RD (local [gallbladder bed]; regional [bile duct, lymph nodes]; distant [discontiguous liver, port site, peritoneal]).
- RESULTS:** Of the 135 patients submitted to re-exploration, RD was found in 82 (61%) overall and in 63 (54%) of 116 patients submitted to resection; the most common site was regional (n = 27, 43%). The T stage of the gallbladder specimen was the only independent predictor of RD (T1b = 35.7%, T2 = 48.3%, T3 = 70%, p = 0.015). The presence of RD at any site dramatically reduced median disease-free survival (DFS) (11.2 vs 93.4 months, p < 0.0001) and disease-specific survival (DSS) (25.2 months vs not reached, p < 0.0001) compared with no RD, respectively. Disease-specific survival did not differ according to RD location, with all anatomic sites being equally poor (p = 0.87). Residual disease at any site predicted DFS (hazard ratio [HR] 3.3, 95% CI 1.9 to 5.7, p = 0.0003) and DSS (HR 2.4, 95% CI 1.2 to 4.6, p = 0.01), independent of all other tumor-related variables.
- CONCLUSIONS:** Survival in patients with RD at local or regional sites was not significantly different than that seen in stage IV disease, with neither subgroup clearly benefiting from reoperation. Outcomes were poor in all patients with RD, regardless of location. (J Am Coll Surg 2014;219:416–429. © 2014 by the American College of Surgeons)
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Incidental gallbladder cancer (IGBCA), or malignancy diagnosed histologically after an elective cholecystectomy for presumed benign disease,^{1,2} is increasing in incidence, a likely consequence of the rising number of elective

cholecystectomies.^{1,3} Re-exploration and definitive resection are recommended for selected patients with invasive tumors and without evidence of disseminated disease. The objective of resection is to treat likely areas of locoregional residual disease (RD). Although it is widely assumed that such operations improve survival,⁴ their benefit has never been demonstrated in prospective studies.

Previous publications have shown RD in up to 72% of patients undergoing re-exploration.⁵⁻⁷ However, disease extent in these studies varies considerably, from gross metastatic disease recognized during re-exploration to unsuspected microscopic disease found only after a complete resection.⁸⁻¹² Lymph node involvement and distant metastases change the disease stage and decrease survival in patients with IGBCA. Likewise, some studies have

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Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
DFS	= disease-free survival
DSS	= disease-specific survival
¹⁸ F-FDG PET-CT	= ¹⁸ F-fluorodeoxyglucose PET-CT
CT	
GBCA	= gallbladder cancer
HR	= hazard ratio
IGBCA	= incidental gallbladder cancer
MSKCC	= Memorial Sloan-Kettering Cancer Center
RD	= residual disease

suggested that RD in the gallbladder fossa also confers reduced survival; however, it has not been defined if all possible areas of RD (ie, local, regional, or distant) have the same impact on survival, especially for patients who do not have macroscopic metastatic disease and undergo complete resection. In addition, it is unknown if the expected decreased survival observed in these patients is a consequence only of stage migration after definitive resection.

The aims of this study were to describe the pattern of RD in patients submitted to complete resection for IGBCA and to determine the impact of the anatomic site of RD on survival. We further sought to correlate preoperative clinical and pathologic variables with the likelihood of RD, and determine if RD was associated with survival.

METHODS

Subjects and data collection

After approval by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (MSKCC), records of all patients with IGBCA who underwent re-exploration between 1998 and 2009 were collected from a prospectively created database and analyzed. This analysis included only patients who underwent a complete or R0 resection of all disease, based on the results of the re-exploration and definitive resection. Recorded data incorporated patient demographics, operative procedures, perioperative outcomes, tumor histopathology and staging, follow-up, recurrence patterns, and survival. Incidental gallbladder cancer was defined as unsuspected gallbladder cancer (GBCA) diagnosed histologically after cholecystectomy performed for presumed benign disease.

The authors' approach to patient selection and evaluation of GBCA has been reported previously.^{2,8,13-15} All patients were restaged with physical examination and imaging studies (thoracic and abdominal/pelvic CT,

MRI, and/or ¹⁸F-fluorodeoxyglucose PET-CT [¹⁸F-FDG PET-CT]), which included those performed at MSKCC and at referring hospitals. Imaging studies were obtained according to surgeon preference and were reviewed at a weekly multidisciplinary hepatopancreatobiliary conference. Re-exploration and definitive resection were recommended to all patients with tumor invasion to at least the muscularis propria layer (T1b) and without evidence of stage IV disease after restaging. Patients with T1a IGBCA were not included in this analysis.

Pathologic examination

The surgical pathology material obtained from the initial cholecystectomy was reviewed before re-exploration to confirm the final diagnosis in all patients and was evaluated for depth of tumor invasion (T stage), tumor histology and grade of differentiation, presence of perineural and/or lymphovascular invasion, inflammation, cystic duct margin, and the presence of adjacent lymph nodes. Tumor involvement of any resection margin was defined as positive. Lymph node metastasis was defined as tumoral involvement in at least 1 lymph node resected. Of note, some patients had involved cystic duct lymph nodes based on analysis of the initial cholecystectomy specimen but had no residual disease found at definitive resection; these patients were classified as N1 but without residual disease. On the other hand, patients with nodal disease after definitive resection were staged as N1 or N2 with residual disease. Depth of tumor invasion and lymph node metastases (N1 vs N2) were defined by the American Joint Committee on Cancer (AJCC) staging manual (7th edition).¹⁶ Of note, in patients with residual disease in the gallbladder fossa, the T stage based on the initial cholecystectomy was maintained because the current AJCC staging system makes no provision for making such changes. Histologic types were divided into adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, and undifferentiated. Histologic differentiation was divided into well, moderately, and poorly differentiated.

Operative approach

The authors' operative approach to resection of GBCA has been documented previously.¹³⁻¹⁵ Staging laparoscopy was performed selectively before laparotomy to exclude metastatic disease.² Patients who appeared to have localized and resectable disease at laparoscopy underwent a laparotomy. Neoadjuvant chemotherapy or chemoradiation was not used in any patient. Open exploration included mobilization and palpation of the liver, duodenum, head of the pancreas, and retroperitoneum, and ultrasonography of the liver. Biopsies were taken of any

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