Published in final edited form as:

J Am Coll Surg. 2014 September ; 219(3): 416–429. doi:10.1016/j.jamcollsurg.2014.01.069.

Residual Disease Predicts Outcomes after Definitive Resection for Incidental Gallbladder Cancer

Jean M Butte, MD¹, T Peter Kingham, MD, FACS¹, Mithat Gönen, PhD², Michael I D'Angelica, MD, FACS¹, Peter J Allen, MD, FACS¹, Yuman Fong, MD, FACS¹, Ronald P DeMatteo, MD, FACS¹, and William R Jarnagin, MD, FACS¹

¹Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

²Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

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 1998-2009 were identified; those submitted to a complete resection were analyzed. Demographics, 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%). 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 to no RD, respectively. DSS did not differ according to RD location, with all anatomic sites being equally poor (p=0.87). RD at any site predicted DFS (HR 3.3, 95% CI 1.9-5.7, p=0.0003) and DSS (HR 2.4, 95% CI 1.2-4.6, p=0.01), independent of all other tumor-related variables.

© 2014 American College of Surgeons. Published by Elsevier Inc. All rights reserved.

Correspondence address: William R. Jarnagin, MD Department of Surgery Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065 Telephone number 212-639-7601 Facsimile number 917-432-2387 jarnagiw@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure Information: Nothing to disclose.

Abstract presented at the annual meeting of the Americas Hepato-Pancreato-Biliary Association, Miami Beach, FL, February 2012.

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. Outcome was poor in all patients with RD, regardless of location.

Keywords

incidental gallbladder cancer; residual disease; survival

INTRODUCTION

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 loco-regional residual disease (RD). While 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 suggested that RD in the gallbladder fossa also confers reduced survival; however, it has not been defined if all possible areas of RD (i.e., local, regional, or distant) have the same impact on survival, especially for those 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 evaluate if RD was associated with survival.

PATIENTS AND 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 includes 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, peri-operative outcomes, tumor histopathology and staging, follow-up, recurrence patterns, and survival. IGBCA 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 re-staged with physical examination and imaging studies [thoracic and abdominal/pelvic computed tomography (CT), magnetic resonance imaging (MRI), and/or ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸FDG PET-CT)], which included those performed at MSKCC and at referring hospitals. Imaging studies were obtained according to surgeon's preference and were reviewed at a weekly multidisciplinary hepatopancreatobiliary conference. Re-exploration and definitive resection was recommended to all patients with tumor invasion to at least the muscularis propria layer (T1b) and without evidence of stage IV disease after re-staging. 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 one 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, since the current AJCC staging system makes no provision for making such changes (see below). 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 prior to laparotomy to exclude metastatic disease.² Patients who appeared to have localized and resectable disease at laparoscopy underwent a laparotomy. Neo-adjuvant chemotherapy/chemo-radiation was not utilized 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 suspicious hepatic or extrahepatic lesions. These were evaluated with frozen-section pathology. Disease was generally considered unresectable if peritoneal or liver metastases (outside of the gallbladder fossa), or involved lymph nodes outside of the porta hepatis basin (i.e., paraduodenal, retropancreatic, common hepatic artery/celiac) were identified. By contrast, involvement of proximal porta hepatis lymph nodes did not necessarily preclude resection.

The extent of liver resection was based on the apparent disease extent and proximity to major inflow pedicles at exploration. Major hepatectomy was defined as a right or left hepatectomy or extended hepatectomy. Minor hepatectomy was defined as resection of segments 4b and 5 or less. Common bile duct resection was performed selectively to achieve clear margins when there was definite or suspected involvement. The lymphadenectomy included nodal tissue in the porta hepatis and portocaval basins and along the common hepatic artery. Port site resection was performed selectively in accordance with surgeon's preference; bile duct resection was performed routinely during the first part of this series, but it is currently performed selectively only when the cystic duct margin is positive and it is not possible to achieve a negative margin. Operative and peri-operative outcomes were recorded. Surgical mortality was defined as death resulting from postoperative complications within 90 days of surgery.

Residual disease

Residual disease after complete resection was defined by intraoperative findings and confirmed by the final pathology report. Specifically, four sites of possible RD were classified: liver (gallbladder bed and/or discontinuous liver involvement), bile duct, regional lymph nodes, and other sites. RD at other sites included peritoneal disease not apparent at the time of definitive resection or involvement of port sites, when these areas were empirically resected; in both of these instances, microscopic distant disease was not suspected during surgery but was identified only after final histologic examination. Local RD included gallbladder bed without discontinuous liver involvement, while regional RD included involvement of bile duct/cystic duct stump and/or regional lymph nodes; distant RD included discontinuous liver involvement (liver metastases), and peritoneal or port site metastases.

Final disease staging was based on the 7th edition of the AJCC manual and included information related to the initial cholecystectomy and re-exploration¹⁶. Patients with incidental nodal or distant disease (i.e., port site or discontinuous liver metastases) were staged accordingly; however, while this staging system clearly defines lymph node involvement and distant metastatic disease, there is no consensus about how the T stage should be classified (or re-classified) in patients who are initially diagnosed with a T1b or T2 IGBCA and subsequently found to have RD in the gallbladder bed.¹⁵ Since it cannot be determined if RD in this setting represents local extension from the primary tumor (i.e., misclassification of the initial T stage), tumor cell spillage from the initial cholecystectomy, or metastatic disease, the original T stage obtained at the time of cholecystectomy was maintained.

Follow-up, recurrence and survival

Disease status at last follow-up was recorded. Disease-specific survival (DSS) was defined as the interval between the date of the definitive operation and the date of last follow-up or death. Only death from disease was considered an event in the analysis of DSS. Disease-free survival (DFS) was defined as the interval between the date of the definitive operation and the date of recurrence or last follow-up in patients without recurrence. One patient was not

considered in the analysis of DFS since the date and pattern of recurrence had not been recorded.

Recurrence was defined as any sign of recurrent disease (clinical, radiographic, and/or pathological). Clinical proof of recurrence was documented by evidence of disease at physical exam (i.e., abdominal mass, lymph node enlargement). All recurrences initially documented clinically were confirmed by biopsy or serial radiology. Radiologic proof of recurrence was documented with sequential imaging demonstrating progression of disease. The impact of RD on cancer-specific survival was assessed, both overall and stratified by site (i.e., local, regional, distant). To further assess the clinical impact of local residual disease, patients with T2N0 GBCA without RD, T3N0 without RD, T1b-2N0 with RD in the gallbladder bed, and T3N0 with RD in the gallbladder bed (i.e., local RD only) were compared.

Statistical analysis

Categorical variables were summarized using proportions, and continuous variables were expressed as the mean ($\pm$ standard deviation) and median (range). Characteristics of patients with residual and no-residual disease were compared using the Fisher exact test for categorical variables and Wilcoxon signed rank test for continuous variables. Survival curves were constructed by the Kaplan-Meier method and were compared using the log-rank test. A univariate Cox proportional hazards regression model was used in all patients treated with complete resection (N=116) to identify factors individually predictive of residual disease and to determine prognostic factors associated with DFS and DSS. All variables that were significant at the 10% level on univariate analysis were entered into a multivariate model using logistic regression, with two exceptions to avoid problems of collinearity: (1) any RD, RD in the liver, bile duct, lymph nodes, or at other sites, and the number of sites affected for RD were highly correlated and only *any RD* was considered in the Cox model; (2) T, N, and M stages and the overall TNM stage were highly correlated and only *TNM stage* was considered in the Cox model. All tests were two-sided and statistical significance was defined as $p < 0.05$. Statistical analysis was performed with SAS version 9.2 and S.P.S.S version 19.0.

RESULTS

Clinical and pathological characteristics before re-exploration

Between 1998 and 2009, 135 patients with IGBCA underwent re-exploration at MSKCC. Nineteen patients had disseminated disease at re-exploration and underwent no further surgical therapy, while complete resection was performed in the 116 (85.9%) patients analyzed in this study. This group includes 81 (69.8%) females, and the median age was 65 years (range, 28–85). Cholelithiasis was diagnosed in 82 patients (70.7%) before surgery and laparoscopic cholecystectomy was performed in the majority of patients (N=87, 75%) (Table 1).

Re-examination of the initial cholecystectomy specimen showed invasion into the perimuscular connective tissue (T2) in most patients (N=62, 53.4%), 108 (93.1%) patients

had adenocarcinoma, and 61 (53.5%) had a moderately differentiated tumor. Lymphovascular invasion was specifically analyzed in 87 patients and was positive in 41 (47.1%); perineural invasion was observed in 42.2% (35 of 83). A positive margin after the initial cholecystectomy was reported in 46 (40%) out of 115 patients and was unknown in 1 patient - the gallbladder bed margin was most commonly involved (N=26), followed by the cystic duct (n = 19) and both in 1 patient. The cystic lymph node was involved by tumor in 13 patients, was benign in 13, and was either not examined or not present in the remainder (Table 1).

All patients (N=116) were re-staged with at least one cross-sectional imaging study before re-exploration: CT was used in 81 patients, MRI/cholangio-MRI in 50 patients, ¹⁸FDG PET-CT in 24 patients, and abdominal ultrasound in 12 patients. Sixty-seven patients were restaged with one modality, 45 with two, and 4 with three.

Definitive treatment

The median time between cholecystectomy and re-exploration was 2 months (range, 0.4-35). Most patients underwent liver resection (N=114, 98.3%), bile duct resection (N=71, 61.2%) and lymphadenectomy (N=116, 100%) as part of their definitive treatment. A combined resection of liver and bile duct was performed in 69 (59.5%) patients, while 2 patients (1.7%) were treated with common bile duct resection and lymphadenectomy (Table 1).

Incidence and location of residual disease

Residual disease was found in 82 of 135 (60.7%) patients with IGBCA submitted to re-exploration and in 63 of 116 (54.3%) patients undergoing resection with curative intent. In this latter subgroup, RD involved the liver in 43 patients (68.3%) (gallbladder bed in 38 and gallbladder bed plus discontinuous liver disease in 5), lymph nodes in 29 patients (46%), common bile duct in 14 patients (22.2%), and other sites in 13 patients (20.6%) [peritoneum (n=6), laparoscopic port sites (n=6), and peritoneum plus port sites (n=1)]. Thirty-eight (60.3%) patients had RD at one site, 16 (25.4%) at two, 7 (11.1%) at three, and 2 (3.2%) at four sites. Residual disease was local-only in 18 patients, regional in 27 patients, and distant in 18 patients; in the latter 18 patients, microscopic metastatic disease was identified only after histologic analysis of the final resected specimen. The TNM staging was as follows: 12 (10.3%) patients were stage I, 38 (32.8%) were stage II, 19 (16.4%) were stage IIIA, 29 (25%) were stage IIIB, and 18 (15.5%) stage IVB.

Comparison of patients with and without RD

Clinical and pathological variables—There were no differences in gender, age, or symptoms before cholecystectomy among patients with (N=63) and without RD (N=53) undergoing resection with curative intent. However, patients with RD had a higher incidence of laparoscopic cholecystectomy converted to open (N=16, 25.4% vs. N=3, 5.7%) (p=0.012), T3 stage tumors (N=28, 44.4% vs. N=12, 22.6%) (p=0.033), and perineural invasion (N=24, 53.3% vs. N=11, 28.9%) (p=0.028) in the cholecystectomy specimen. The median time between cholecystectomy and re-exploration was similar among patients with and without RD (2 months, range 1-35 vs. 2 months, range 0.4-7) (p=0.3). Not surprisingly,

patients with RD had a significantly higher TNM stage compared to patients without RD ($p<0.0001$) (Table 1).

Treatment-related variables—Common bile duct resection was performed more commonly in patients with RD (N=47, 74.6%) compared those without (N=24, 45.3%) ($p=0.002$). By contrast, the extent of liver resection ($p=0.058$), extra-hepatic resection ($p=0.5$), operative blood loss ($p=0.16$), length of hospital stay ($p=0.06$) and postoperative complications ($p=0.5$) did not differ between the groups. Adjuvant therapy was more commonly administered to patients with RD than without RD [N=22 (34.9%) vs. N=2 (3.8%)], respectively, $p<0.0001$ (Table 1).

Patients with RD identified at local, regional, and distant sites did not differ in terms of clinical, pathological, and treatment-related variables (Table 2).

Follow-up, recurrence, and survival

Following definitive resection, 65 of 116 patients (56%) recurred at a median time of 11 months (range, 2-127). Recurrence was significantly more frequent in patients with RD (N=46, 73%) compared to patients without RD (N=19, 35.8%) ($p<0.0001$). However, the pattern of disease recurrence after definitive resection was similar ($p=0.4$) (Table 3). The final status after a median follow-up of 27.3 months (range, 0.4-170.3) was as follows: 56 patients were dead of disease, 42 had no evidence of disease, 9 were alive with disease, 4 died of unknown causes, 3 died of other causes, and 2 died of postoperative complications.

Median DFS was 25.9 months (95% CI, 13-38.8) (Figure 1A), and was higher in those patients without RD (median, 93.4 months; 95% CI, 67.1-119.7) compared to patients with RD (median, 11.2 months; 95% CI, 6.9-15.5) (Figure 1B, $p<0.0001$). Median DSS was 42.8 months (95% CI, 21.3-64.3) (Figure 1C), and was also higher in those patients without RD (median not reached) compared to patients with RD (median, 25.2 months; 95% CI, 14.8-35.6) (Figure 1D, $p<0.0001$). Of note, DFS did not differ among patients with residual disease in local (median, 9.3 months; 95% CI, 6.8-11.8), regional (median, 16.8 months; 95% CI, 7-26.7) or distant sites (median, 8.7 months; 95% CI, 3.4-13.9), ($p=0.25$) (Figure 2A). Similarly, DSS did not differ based on site of recurrence: local (median, 39.2 months; 95% CI, 11.5-66.9), regional (median, 30.9 months; 95% CI, 17.3-44.4), distant (median, 23.8 months; 95% CI, 14.8-32.8) ($p=0.87$) (Figure 2B).

To fully assess the impact of local RD on survival, patients with and without RD were compared directly. For the purposes of this analysis, patients with T2N0 (N=30) and T3N0 (N=9) tumors and no RD were compared to patients with comparable T stage and local RD (i.e., gallbladder fossa) only. Median DFS of patients with a T2N0 GBCA and no RD was not reached, and was 93.4 months (95% CI, 0-235 months) in patients with a T3N0 GBCA and no RD; by contrast, in patients with local RD, DFS was 32 months (95% CI, 4.6-59.5 months) patients with a T1b-2N0 tumors and 5.6 months (95% CI, 4.4-6.8 months) in patients with T3N0 disease ($p<0.0001$). The median DSS was not reached in patients with T2N0 or T3N0 GBCA and no RD, while it was 22 months (95% CI, 0-58 months) in patients with a T1b-2N0 and local RD, and 17.7 months (95% CI, 0-51.5 months) in patients with a T3N0 and local RD ($p=0.003$) (Figure 3).

Univariate and multivariate analyses to predict RD, DFS, and DSS

Residual disease—The univariate analysis of patients treated with complete resection (N=116) is shown in Table 4. Of note, the type of cholecystectomy was significantly correlated with T stage ($p=0.001$). Multivariate analysis showed that T stage was the only independent predictor factor of RD ($p=0.015$) (OR 2.7, 95% CI 1.21-6.1) (Table 4).

Disease-free survival—The univariate analysis included 115 patients and is shown in Table 5. One patient was excluded because the time to recurrence was not known. Multivariate analysis showed that tumor grade or differentiation (HR 4.0, 95% CI 1.55-10.8) ($p=0.03$) and any RD (HR 3.3, 95% CI 1.9-5.7) ($p=0.0003$) were independent predictors factors of DFS (Table 5).

Disease-specific survival—This analysis included 116 patients and is shown in Table 5. The multivariate analysis showed that tumor grade or differentiation (HR 5.5, 95% CI 1.64-18.2) ($p=0.0009$), any RD (HR 2.4, 95% CI 1.2-4.6) ($p=0.01$), and positive lymph nodes (HR 2.24, 95% CI 1.2-3.99) were independent predictors factors of DSS (Table 5).

DISCUSSION

The incidence of IGBCA after cholecystectomy for presumed benign disease has increased during the past several years and currently is a common presentation.^{14, 17} Re-exploration and definitive resection are recommended in select patients who do not present with any evidence of disseminated disease at re-staging.¹⁸⁻²⁰ The goals of resection are, first, to improve survival by resecting all areas of possible RD, and second, to stage the disease completely.^{4, 21}

The population of the present study was similar to that of previous publications of IGBCA.^{6, 22-24} Of the patients who underwent laparoscopic cholecystectomy for gallstones and were diagnosed with an adenocarcinoma invading the perimuscular connective tissue, most were female. More importantly, a high incidence (61%) of RD was observed in patients undergoing definitive surgery and in those who were treated with curative intent (55%). Most patients had RD involving the gallbladder bed, followed by lymph nodes, and common bile duct. These findings also confirmed that although intraoperative evaluation is a key element of the staging process and for determining the extent of required surgery (i.e., resection of common bile duct), the real extent of disease is often only determined by the final pathologic analysis. This is evident in that 19 (16.4%) patients had unsuspected distant metastases on final pathologic examination in the liver, port sites, or peritoneum after undergoing complete resection.

Two previous multicenter studies have shown a similar rate and location of RD.^{6, 7} The first evaluated 115 patients with IGBCA treated at 6 centers of North and South America, and Europe;⁶ the second included 188 patients (148 treated with complete resection) who underwent reexploration at 21 centers of France.⁷ RD was found in 60.8% of and 64% of patients, respectively, and mainly involved lymph nodes, common bile duct, and the liver. However, the present study differs from these two studies in several aspects. This is the largest series from a single center, which compared to multicenter studies, decreases bias

related to patient selection and treatment and allows for a more thorough assessment of outcomes. In addition, this is the first study that definitively establishes T stage as an independent predictor of RD and the presence of any RD as an independent determinant of survival in patients with IGBCA, using multivariate analysis with adequate follow-up.

The major finding of this study was that in patients with IGBCA submitted to definitive reoperation and resection, RD at any site was associated with an equally poor outcome with respect to cancer recurrence and survival. The adverse impact of residual cancer in regional lymph nodes or at distant sites on outcome is not surprising, since these findings necessarily change the stage of disease. By contrast, local RD within the gallbladder fossa is not associated with any change in disease stage, and yet survival in this patient subgroup was no different than that observed in patients with regional or distant RD. Other studies have shown that local RD adversely impacts survival,^{6, 10} but this is the first analysis to show that RD at local or regional sites reduces overall survival to that seen in stage IV disease. Likewise, the differences in survival based on location of RD, while not significant in the present analysis, require confirmation in larger series to ensure against the confounding influence of Type 2 error.

The current study raises concerns regarding the current staging and treatment approach in patients with IGBCA. Residual disease in the liver bed, particularly in the setting of T2 tumors, would suggest inaccuracies in the initial assessment of the T stage or the presence of metastatic disease. In a study of 20 patients with T2 invasive tumors submitted to single-stage resection, Endo et al.²⁵ showed that 25% had discontinuous microscopic disease within the liver parenchyma, which was associated with a significant reduction in survival. Similar results were reported by Wakai et al.²⁶ in a larger series of patients submitted to a single-stage resection. In the setting of a 2-stage resection, it is impossible to know if local RD is the result of metastatic disease or more advanced T stage, unrecognized on initial assessment. Regardless of the mechanism, the presence of RD at both local and regional sites seems to be the clinical equivalent of distant metastatic disease. The absence of any survival difference among the subgroups stratified by RD location supports this assertion.

The results are both surprising and disappointing, since the goal of reoperation and resection in this setting is clearance of residual local/regional disease; however, the efficacy of resection alone in patients with known RD is now called into question. Although this study does not specifically analyze the role of neo-adjuvant and adjuvant therapies in gallbladder cancer, the data would suggest consideration of a change in treatment approach in patients with RD, given the high risk of recurrence and death. At the very least, adjuvant chemotherapy, previously not used routinely in this setting, should be examined in prospective trials as a means of improving outcome. Alternatively, a neo-adjuvant approach, targeting patients with a high risk of having RD, might help select patients most likely to benefit from reoperation and definitive resection.

Whatever approach is ultimately adopted, it is clear that resection alone is inadequate therapy in many patients. Neoadjuvant therapy is attractive for many reasons, particularly as it may spare some patients an unnecessary operation; however, non-operative identification of RD may represent a challenge in many patients. The T stage of the initial

cholecystectomy was the most powerful predictor and the only independent predictor of RD (T3=70%, T2=48.3%, and T1b=35.7%; $p=0.015$), and while potentially useful for identifying high-risk patients, it is clearly imperfect. Other clinical variables that might help stratify patients include type of cholecystectomy (laparoscopic converted to open), positive cholecystectomy margin, and poor differentiation.⁶

Several limitations of this analysis must be recognized. First and foremost, the question of whether reoperation is appropriate for patients with gross local or regional RD, although suggested by the data presented, cannot be answered by the current study, given its retrospective nature and the absence of a control group. Indeed, the weight of published evidence supports reoperation and definitive resection as the most effective therapy; the current study does not change this recommendation but rather points out its limitations and argues for a re-evaluation of current treatment recommendations. Second, this single-center has the typical advantage of using data from patients whose standards of care followed institutional standards that varied minimally from one patient to another. This results in less noise and a higher chance to correctly identify risk factors. Generalizability of our findings to other hospitals will depend on how patient selection and treatment criteria differs from one center to the other. Third, the initial analysis of the gallbladder specimen was frequently performed elsewhere, after an incidental diagnosis, and although all specimens were re-examined by pathologists at MSKCC, potential inaccuracies in T-stage assessment, although unlikely, cannot be entirely excluded. In addition, the number of patients in each T stage was low, and the results must be confirmed in larger cohorts.

In conclusion, this is the largest series from a single center that evaluates predictors of RD in IGBCA and its role as a prognostic factor of DFS and DSS. Analysis of findings related to the initial cholecystectomy and a complete review of gallbladder specimen, specifically T stage, tumor differentiation, and perineural invasion can help to predict the risk of RD. Patients with RD after re-exploration and definitive resection had an increased risk of recurrence and a decreased DFS and DSS, and this was true for RD at all sites. RD at local and regional sites was the clinical equivalent of stage IV disease. The results call into question the current staging of IGBCA and suggest a re-evaluation of the current treatment approach in patients with RD.

Acknowledgments

Funding: This study was supported by NIH/NCI Cancer Center Support Grant P30 CA008748.

LIST OF ABBREVIATIONS

RD	residual disease
IGBCA	incidental gallbladder cancer
DFS	disease-free survival
DSS	disease-specific survival
MSKCC	Memorial Sloan-Kettering Cancer Center

GBCA	gallbladder cancer
CT	computed tomography
MRI	magnetic resonance imaging
¹⁸FDG PET-CT	¹⁸ F-fluorodeoxyglucose positron emission tomography-computed tomography
AJCC	American Joint Committee on Cancer

REFERENCES

1. Hueman MT, Vollmer CM Jr, Pawlik TM. Evolving treatment strategies for gallbladder cancer. *Ann Surg Oncol*. 2009; 16(8):2101–15. [PubMed: 19495882]
2. Butte JM, Gönen M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB (Oxford)*. 2011; 13(7):463–72. [PubMed: 21689230]
3. Jin K, Lan H, Zhu T, et al. Gallbladder carcinoma incidentally encountered during laparoscopic cholecystectomy: how to deal with it. *Clin Transl Oncol*. 2011; 13(1):25–33. [PubMed: 21239352]
4. Mayo SC, Shore AD, Nathan H, et al. National trends in the management and survival of surgically managed gallbladder adenocarcinoma over 15 years: a population-based analysis. *J Gastrointest Surg*. 2010; 14(10):1578–91. [PubMed: 20824371]
5. Butte JM, Waugh E, Meneses M, et al. Incidental gallbladder cancer: analysis of surgical findings and survival. *J Surg Oncol*. 2010; 102(6):620–5. [PubMed: 20721958]
6. Pawlik TM, Gleisner AL, Vigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg*. 2007; 11(11):1478–86. discussion 1486–7. [PubMed: 17846848]
7. Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFCGBC-2009 Study Group. *World J Surg*. 2011. 35(8):1887–97.
8. Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol*. 2012; 19(2):409–17. [PubMed: 21698501]
9. Cavallaro A, Piccolo G, Panebianco V, et al. Incidental gallbladder cancer during laparoscopic cholecystectomy: Managing an unexpected finding. *World J Gastroenterol*. 2012; 18(30):4019–27. [PubMed: 22912553]
10. Lendoire JC, Gil L, Duek F, et al. Relevance of residual disease after liver resection for incidental gallbladder cancer. *HPB (Oxford)*. 2012; 14(8):548–53. [PubMed: 22762403]
11. Choi SB, Han HJ, Kim CY, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. *World J Surg*. 2009; 33(12):2657–63. [PubMed: 19823903]
12. Glauser PM, Strub D, Kaser SA, et al. Incidence, management, and outcome of incidental gallbladder carcinoma: analysis of the database of the Swiss association of laparoscopic and thoracoscopic surgery. *Surg Endosc*. 2010; 24(9):2281–6. [PubMed: 20177918]
13. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol*. 2009; 16(4):806–16. [PubMed: 18985272]
14. Butte JM, Matsuo K, Gönen M, et al. Gallbladder cancer: differences in presentation, surgical treatment, and survival in patients treated at centers in three countries. *J Am Coll Surg*. 2011; 212(1):50–61. [PubMed: 21075015]
15. Ito H, Ito K, D'Angelica M, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann Surg*. 2011; 254(2):320–5. [PubMed: 21617582]
16. Edge SB, BD.; Compton, CC. *AJCC Cancer Staging Manual*. 7th ed.. Springer; New York, NY: 2010. Gallbladder cancer.; p. 211–7.
17. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol*. 2008; 98(7):485–9. [PubMed: 18802958]

18. Bartlett DL, Fong Y, Fortner JG, et al. Long-term results after resection for gallbladder cancer. Implications for staging and management. *Ann Surg.* 1996; 224(5):639–46. [PubMed: 8916879]
19. Choi SB, Han HJ, Kim CY, et al. Surgical outcomes and prognostic factors for T2 gallbladder cancer following surgical resection. *J Gastrointest Surg.* 2010; 14(4):668–78. [PubMed: 20033339]
20. Dai M, Fong Y, Lowy A. Treatment of T3 gallbladder cancer. *J Gastrointest Surg.* 2009; 13(11): 2040–2. [PubMed: 19194769]
21. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer.* 2003; 98(8):1689–700. [PubMed: 14534886]
22. Eslick GD. Epidemiology of gallbladder cancer. *Gastroenterol Clin North Am.* 2010; 39(2):307–30. ix. [PubMed: 20478488]
23. Fong Y, Heffernan N, Blumgart LH. Gallbladder carcinoma discovered during laparoscopic cholecystectomy: aggressive reresection is beneficial. *Cancer.* 1998; 83(3):423–7. [PubMed: 9690533]
24. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg.* 2000; 232(4):557–69. [PubMed: 10998654]
25. Endo I, Shimada H, Takimoto A, et al. Microscopic liver metastasis: prognostic factor for patients with pT2 gallbladder carcinoma. *World J Surg.* 2004; 28(7):692–6. [PubMed: 15175901]
26. Wakai T, Shirai Y, Sakata J, et al. Mode of hepatic spread from gallbladder carcinoma: an immunohistochemical analysis of 42 hepatectomized specimens. *Am J Surg Pathol.* 2010; 34(1): 65–74. [PubMed: 19956061]

Precis

The relevance of residual disease with respect to location is not well defined. This study showed that disease-free survival and disease-specific survival were poor in all patients with residual disease, regardless of location, and were similar to that seen in stage IV disease. These findings suggest the need for an adjuvant or neo-adjuvant treatment.

Figure 1.

(A) Disease-free survival (DFS) of all patients undergoing R0 resection (N=115), (B) Comparison of DFS between patients with and without residual disease (RD), (C) Disease-specific survival (DSS) of all patients undergoing R0 resection (N=116), and (D) Comparison of DSS between patients with and without RD. NRD, no residual disease.

Figure 2.

Comparison of (A) Disease-free survival and (B) disease-specific survival according to location of residual disease (RD) (local, regional, and distant). NRD, no residual disease.

Figure 3.

Comparison of disease-free survival between patients with T2N0 GBCA without residual disease (RD), T3N0 without RD, T1b-2N0 presenting with RD only in the gallbladder bed, and T3N0 with RD only in the gallbladder bed. NRD, no residual disease.

Table 1

Comparison of Clinical, Pathologic, and Treatment-Related Variables between Patients With and Without Residual Disease

	Total, n=116, n (%)	Residual disease, n=63, n (%)	No residual disease, n=53, n (%)	p Value
Female sex, n (%)	81 (69.8)	44 (69.8)	37 (69.8)	1.0
Age, y				0.3
Mean $\pm$ SD	64 $\pm$ 10.3	63 $\pm$ 11	65 $\pm$ 9.3	
Median (range)	65 (28-85)	63.5 (28-83)	65 (42-85)	
Gallstones	82 (70.7)	40 (63.5)	42 (79.2)	
Acute cholecystitis	72 (62.1)	37 (58.7)	35 (66)	
Type of cholecystectomy				0.012
Laparoscopic	87 (75)	41 (65.1)	46 (86.8)	
Laparoscopic converted	19 (16.4)	16 (25.4)	3 (5.7)	
Open	10 (8.6)	6 (9.5)	4 (7.5)	
T				0.033
1b	14 (12.1)	5 (7.9)	9 (17)	
2	62 (53.4)	30 (47.6)	32 (60.4)	
3	40 (34.5)	28 (44.4)	12 (22.6)	
Histology				0.36
Adenocarcinoma	108 (93.1)	58 (92.1)	50 (94.3)	
Adenosquamous	7 (6)	5 (7.9)	2 (3.8)	
Squamous	1 (0.9)	0	1 (1.9)	
Grade				0.14
Well	15 (13.2)	6 (9.8)	9 (17)	
Moderately	61 (53.5)	30 (49.2)	31 (58.5)	
Poorly	38 (33.3)	25 (41)	13 (24.5)	
Presence of LVI	41 (47.1)	24 (52.2)	17 (42.5)	0.39
Presence of PNI	35 (42.2)	24 (53.3)	11 (28.9)	0.028
Positive margin (cholecystectomy)	46 (39.6)	30 (48.4)	16 (30.2)	0.057
Time between operations, mo				0.3
Mean $\pm$ SD	2.2 $\pm$ 3.4	2.5 $\pm$ 4.5	1.9 $\pm$ 1.1	
Median (range)	2 (0.4-35)	2 (1-35)	2 (0.4-7)	
Type of resection				0.058
Segmentectomy 4b+5	82 (70.7)	41 (65.1)	41 (77.4)	
Hepatectomy + extended hepatectomy	32 (27.6)	22 (34.9)	10 (18.9)	
Bile duct resection alone	2 (1.7)	0	2 (3.8)	
Hepatic resection	114 (98.3)	63 (100)	51 (96.2)	0.2
Bile duct resection	71 (61.2)	47 (74.6)	24 (45.3)	0.002
Extra-hepatic resection	9 (7.8)	6 (9.5)	0.23 (5.7)	0.5

	Total, n=116, n (%)	Residual disease, n=63, n (%)	No residual disease, n=53, n (%)	p Value
Time, min				0.36
Mean $\pm$ SD	277 $\pm$ 92	289 $\pm$ 78	263 $\pm$ 106	
Median (range)	270 (111-720)	280 (160-530)	235 (111-720)	
Blood loss, mL				0.16
Mean $\pm$ SD	448 $\pm$ 435	498 $\pm$ 514	384 $\pm$ 307	
Median (range)	300 (10-3000)	334 (10-3000)	300 (50-1900)	
Postoperative complications	35 (30.2)	21 (33.3)	14 (26.4)	0.5
Length of hospital stay, d				0.06
Mean $\pm$ SD	10.6 $\pm$ 6.2	11.6 $\pm$ 7	9.4 $\pm$ 5	
Median (range)	9(4-37)	9 (5-37)	8 (4-28)	
TNM				<0.0001
I	12 (10.3)	3 (4.8)	9 (17)	
II	38 (32.8)	8 (12.7)	30 (56.6)	
IIIA	19 (16.4)	10 (15.9)	9 (17)	
IIIB	29 (25)	24 (38.1)	5 (9.4)	
IVB	18 (15.5)	18 (28.6)	0	
Adjuvant treatment	24 (20.7)	22 (34.9)	2 (3.8)	

LVI, lymphovascular invasion, PNI, perineural invasion.

Table 2

Comparison of Clinical, Pathologic and Treatment-Related Variables Stratified by Location of Residual Disease

	Total, n=63, n (%)	RD Local, n=18, n (%)	RD Regional, n=27, n (%)	RD Distant, n=18, n (%)	p Value
Sex, female	44 (69.8)	12 (66.7)	20 (74.1)	12 (66.7)	0.8
Age, y					0.9
Mean $\pm$ SD	63.2 $\pm$ 11	62.6 $\pm$ 9.6	63 $\pm$ 12.6	64 $\pm$ 10.4	
Median (range)	64 (28-83)	62 (41-80)	64 (28-83)	65 (41-81)	
Gallstones	40 (63.5)	10 (55.6)	19 (70.4)	11 (61.1)	0.5
Acute cholecystitis	37 (59.7)	11 (61.1)	14 (53.8)	12 (66.7)	0.6
Type of cholecystectomy					0.5
Laparoscopic	41 (65.1)	9 (50)	19 (70.4)	13 (72.2)	
Laparoscopic converted	16 (25.4)	7 (38.9)	5 (18.5)	4 (22.2)	
Open	6 (9.5)	2 (11.1)	3 (11.1)	1 (5.6)	
T					0.6
1b	5 (7.9)	1 (5.6)	3 (11.1)	1 (5.6)	
2	30 (47.6)	7 (38.9)	15 (55.6)	8 (44.4)	
3	28 (44.4)	10 (55.6)	9 (33.3)	9 (50)	
Histology					0.5
Adenocarcinoma	58 (92.1)	16 (88.9)	26 (96.3)	16 (88.9)	
Adenosquamous	5 (7.9)	2 (11.1)	1 (3.7)	2 (11.1)	
Grade					0.2
Well	6 (9.8)	0	5 (19.2)	1 (5.6)	
Moderately	30 (49.2)	9 (52.9)	11 (42.3)	10 (55.6)	
Poorly	25 (41)	8 (47.1)	10 (38.5)	7 (38.9)	
Presence of LVI	24 (52.2)	10 (66.7)	8 (50)	7 (38.9)	0.3
Presence of PNI	24 (53.3)	5 (33.3)	11 (68.8)	8 (57.1)	0.1
Positive margin (cholecystectomy)	30 (48.4)	10 (55.6)	11 (42.3)	9 (50)	0.6
Time between operations, mo					0.06
Mean $\pm$ SD	2.4 $\pm$ 4.5	1.5 $\pm$ 0.9	1.6 $\pm$ 0.7	4.5 $\pm$ 8.1	
Median (range)	1.5 (0.6-35)	1.2 (0.6-4.3)	1.5 (0.6-3.1)	1.6 (1-35)	
Type of resection					0.5
Segmentectomy 4b+5	41 (65.1)	10 (55.6)	18 (66.7)	13 (72.2)	
Hepatectomy	19 (29.7)	8 (44.4)	9 (33.3)	5 (27.8)	
Bile duct resection	47 (74.6)	13 (72.2)	19 (70.4)	15 (83.3)	0.6
Extra-hepatic resection	6 (9.5)	3 (16.7)	2 (7.4)	1 (5.6)	0.4
Adjuvant treatment	22 (34.9)	5 (27.8)	10 (37)	7 (38.9)	0.7
Recurrence	46 (73)	14 (77.8)	17 (63)	15 (83.3)	0.2

RD, residual disease; LVI, lymphovascular invasion; PNI, perineural invasion.

Table 3

Evaluation of Recurrence and Pattern of Recurrence in All Patients

	Total, n=116, n (%)	Residual disease, n=63, n (%)	No residual disease, n=53, n (%)	p Value
Recurrence				<0.0001
Yes	65 (56)	46 (73)	19 (35.8)	
No	51 (44)	17 (27)	34 (64.2)	
Pattern of recurrence				0.4
* n	64	45	19	
Local	9 (14.1)	6 (13.3)	3 (15.8)	
Distant	51 (79.7)	35 (77.8)	16 (84.2)	
Local + distant	4 (6.2)	4 (8.9)	0	

* One patient without information.

Table 4

Univariate and Multivariate Analysis of Variables Associated with Residual Disease in Patients with Incidental Gallbladder Cancer Who Underwent Complete Resection

Variable	n=116	No residual disease, n=53, n (%)	Residual disease, n=63, n (%)	p Univariate	p Multivariate	Odds Ratio	95% CI
Female sex	81	37 (45.7)	44 (54.3)	1.0			
Age, y				0.7			
65	62	27 (43.5)	35 (56.5)				
> 65	54	26 (48.1)	28 (51.9)				
Acute cholecystitis	72	35 (48.6)	37 (51.4)	0.5			
Emergency cholecystectomy	62	29 (46.8)	33 (53.2)	1.0			
Type of cholecystectomy				0.009			
Open	10	4 (40)	6 (60)				
Laparoscopic converted to open	19	3 (15.8)	16 (84.2)				
Laparoscopic	87	46 (52.9)	41 (47.1)				
T stage				0.03	0.015	2.7	1.21-6.1
1b + 2	76	41 (54)	35 (46)				
3	40	12 (30)	28 (70)				
Inflammation	78	35 (44.9)	43 (55.1)	0.8			
Gallstones	106	48 (45.3)	58 (54.7)	1.0			
Tumor type				0.3			
Adenocarcinoma	108	50 (46.3)	58 (53.7)				
Adenosquamous	7	2 (28.6)	5 (71.4)				
Squamous	1	1 (100)	0				
Grade				0.1			
Well	15	9 (60)	6 (40)				
Moderately	61	31 (50.8)	30 (49.2)				
Poorly	38	13 (34.2)	25 (65.8)				
Lymph node status				0.9			
Negative	13	6 (46.2)	7 (53.8)				
Positive	13	5 (38.5)	8 (61.5)				

Variable	n=116	No residual disease, n=53, n (%)	Residual disease, n=63, n (%)	p Univariate	p Multivariate	Odds Ratio	95% CI
Unknown	90	42 (46.7)	48 (53.3)				
Presence of lymphovascular invasion	41	17 (41.5)	24 (58.5)	0.4			
Presence of perineural invasion	35	11 (31.4)	24 (68.6)	0.03			
Positive cholecystectomy margin	46	16 (34.8)	30 (65.2)	0.05			
No. studies suggesting residual disease				0.4			
Mean $\pm$ SD	0.33 $\pm$ 0.57	0.26 $\pm$ 0.52	0.35 $\pm$ 0.6				
Median (range)	0 (0-2)	0 (0-2)	0 (0-2)				
Time between surgeries, mo				0.8			
Mean $\pm$ SD	2.2 $\pm$ 3.4	1.9 $\pm$ 1.1	2.5 $\pm$ 4.5				
Median (range)	2 (0.4-35)	2 (0.4-7)	2 (1-35)				

Table 5

Univariate and Multivariate Analysis of Prognostic Factors Associated with Disease-Free Survival and Disease-Specific Survival for Patients with Incidental Gallbladder Cancer Who Underwent Complete Resection

Variable	DFS, n	Median DFS,	UV p	MV p	HR (95% CI)	DSS N	Median DSS (months)	UV p	MV p	HR (95% CI)
Female sex	80	24	0.74			81	48	0.4		
Age, y			0.7					0.5		
65	61	19				62	33			
> 65	54	32				54	43			
Acute cholecystitis	71	26	0.8			72	40	0.3		
Emergency cholecystectomy	61	26	0.7			62	42	0.5		
Type of cholecystectomy			0.09					0.35		
Open	9	39				10	39			
Laparoscopic converted to open	19	11				19	31			
Laparoscopic	87	32				87	48			
Gallstones	105	24	0.3			106	42	0.1		
Microscopic inflammation	78	24	0.4			78	40	0.18		
Tumor type			0.4					0.2		
Adenocarcinoma	107	32				108	48			
Adenosquamous	7	9				7	14			
Squamous	1	NA				1	NA			
Grade			0.009	0.03				0.002	0.0009	
Well	14	110			1	15	NA			1
Moderately	61	22			2.7 (1.05-7.2)	61	48			3.5 (1.06-11.6)
Poorly	38	13			4.0 (1.55-10.8)	38	31			5.5 (1.64-18.2)
Presence of lymphovascular invasion	41	18	0.6			41	39	0.1		
Presence of perineural invasion	34	13	0.08			35	24	0.015		
Positive cholecystectomy margin	45	11	0.0002			46	32	0.006		
Time between operations, mo			0.7					0.4		
1	54	32				55	62			
> 1	60	26				61	39			

Variable	DFS, n	Median DFS,	UV p	MV p	HR (95% CI)	DSS N	Median DSS (months)	UV p	MV p	HR (95% CI)
Main procedure during re-exploration			0.3					0.4		
Segmentectomy 4b + 5	82	26				82	42			
Hepatectomy	31	19				32	42			
Bile duct resection alone	2	NA				2	NA			
Hepatic resection	113	24	0.1			114	42	0.2		
Segmentectomy	92	24	0.6			93	40	0.4		
Bile duct resection	70	22	0.7			71	48	0.9		
Extrahepatic resection	9	8.5	0.5			9	80	0.85		
Blood loss			0.9					0.9		
300	57	32				57	43			
> 300	55	22				56	40			
Postoperative complications	34	32	0.46			35	62	0.3		
Margin after curative intent surgery			0.3					0.2		
R0	114	2				114	43			
R1	1	NA				2	24			
Residual disease (any)			<0.0001	0.0003				<0.001	0.01	
Yes	62	11			3.3 (1.9-5.7)	63	24			2.4 (1.2-4.6)
No	53	93			1	53	NA			1
Residual disease (liver)			<0.0001					<0.001		
Yes	43	10				43	22			
No	72	93				73	NA			
Residual disease (bile duct)			0.07					0.1		
Yes	13	11				13	24			
No	102	32				103	43			
Residual disease (lymph nodes)			0.02					0.002		
Yes	29	15				29	24			
No	86	39				87	62			
Residual disease (other sites)			0.036					0.06		
Yes	13	11				13	24			

Variable	DFS, n	Median DFS,	UV p	MV p	HR (95% CI)	DSS N	Median DSS (months)	UV p	MV p	HR (95% CI)
No	102	32				103	62			
Residual disease (number of sites)			<0.0001					<0.001		
0	53	93				53	NA			
1	37	13				38	39			
2	16	11				16	24			
3	7	9				7	18			
4	2	18.5				2	67			
T stage			<0.0001					0.002		
1b	13	NA				14	NA			
2	62	41				62	62			
3	40	10				40	31			
N stage			0.003					0.0001	0.006	
Positive	37	15				37	24			2.24 (1.2-3.99)
Negative	78	41				79	70			1
M stage			0.0001					0.008		
M0	97	35				98	62			
M1	18	9				18	21.5			
TNM stage*			<0.001					<0.001		
Stage I	11	NA				11	NA			
Stage II	38	NA				38	NA			
Stage IIIA	19	11				19	40			
Stage IIIB	29	17				29	31			
Stage IVB	18	9				19	21.5			

DFS, disease-free survival; DSS, disease-specific survival; MV, multivariate; UV, univariate.

* In multivariate analysis, TNM stage was dichotomized as I-II vs higher to accommodate the number of events.