Ann Surg Oncol (2009) 16:806–816
DOI 10.1245/s10434-008-0189-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

Analysis of the Extent of Resection for Adenocarcinoma of the Gallbladder

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ABSTRACT Gallbladder cancer has historically been considered an incurable malignancy; although, extended resection has been associated with cure in selected patients. However, the optimal extent of resection is unknown. The objective of this study was to analyze the impact of the extent of resection for gallbladder adenocarcinoma on disease-specific survival (DSS) and perioperative morbidity. Analysis of a prospective hepatobiliary surgery database identified patients undergoing surgical resection for gallbladder adenocarcinoma from 1990 to 2002. Clinicopathologic factors including extent of resection were analyzed for their association with DSS and perioperative morbidity. Long-term outcome was evaluable in 104 patients. With median follow-up of 58 months for survivors, the actuarial 5-year DSS was 42%. Thirty-six patients (35%) underwent major hepatectomy, but in 15 this was not mandatory to clear all disease. Sixty-eight patients (65%) underwent common bile duct (CBD) excision, but 32 were performed empirically. Twenty-one patients (20%) underwent en bloc resection of adjacent organs other than the liver. The performance of a major hepatectomy or a CBD excision was not associated with other clinicopathologic variables or long-term survival. Resection of adjacent organs were associated with advanced T stage but not with survival. T stage, N stage, histologic differentiation, and CBD involvement were independently associated with survival. Major hepatectomy and CBD excision were significantly associated with perioperative morbidity. We conclude that tumor biology and stage, rather than extent of resection, predict outcome after resection for gallbladder cancer. Major hepatic resections, including major hepatectomy and CBD excision, are appropriate when necessary to clear disease but are not mandatory in all cases.

Adenocarcinoma of the gallbladder has historically been considered an incurable malignancy with dismal prognosis due to its propensity for early dissemination. In a literature review from 1978, the authors reported 5% 5-year survival and median survival of 5–8 months for 5,836 cases.[1] For the 25% of patients who underwent a potentially curative operation, only 16.5% survived 5 years. However, in recent years, surgical treatment has been associated with cure in some patients, and this cure rate is highly correlated to stage.[2,3] In the rare case of a T1a tumor (primary not invading the lamina propria or muscularis), simple cholecystectomy is curative in over 90% of cases. Unfortunately, these tumors are only found incidentally in cholecystectomy specimens performed for other reasons. For the remainder of nonmetastatic gallbladder cancers, a simple cholecystectomy has been associated with poor outcome. However, extended cholecystectomy, which includes resection of the adjacent liver tissue and portal lymphadenectomy, has been associated with improved survival and cure and is considered standard of care.[3]

The extent of resection performed for gallbladder cancer has a wide range. George Pack first advocated radical liver resection as treatment for gallbladder cancer in 1955, reporting a right hemihepatectomy and portal lymphadenectomy.[4] As the safety of hepatic resections and biliary reconstructions have improved, such major resections are increasingly performed for gallbladder cancer.[5–9] Today, a partial hepatectomy involving the gallbladder fossa is a critical part of the resection, but can range from a wedge

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First Received: 11 July 2008;
Published Online: 5 November 2008

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resection to an anatomic resection of segments 4b and 5 to an extended right hepatectomy. From a vascular standpoint, if a tumor is adherent to the right-sided hepatic inflow structures, an extended right hepatectomy would be mandated for a complete resection. Conversely, if a major hepatectomy is not required by tumor location, the optimal extent of the hepatectomy has not been well studied. Only one small study compared outcomes of 11 patients undergoing extended hepatectomy (some mandated by tumor extent) with outcomes of 11 patients undergoing a lesser resection, and found no difference in long-term survival.[10] In a similar fashion, excision of the extrahepatic bile duct is sometimes necessary because of tumor or nodal involvement; however, the impact of routine excision of the bile duct to enhance nodal dissection and resect occult disease has only been studied in very small numbers. While some groups have found bile duct excision to be associated with improved survival, others have found no difference.[11–14] Finally, if tumor extension and adhesions from prior surgery involve adjacent organs, mandating resection of these organs, extensive resection to include these organs is necessary; however, outcome in this situation is also poorly documented.

In this study, we aimed to analyze the extent of resection performed for gallbladder cancer, its indications, and its association with survival and perioperative morbidity. In particular, we analyzed the role of major hepatectomy, bile duct resection, and adjacent organ resection.

PATIENTS AND METHODS

From October 1988 through 2002, all adult patients from Memorial Sloan-Kettering Cancer Center (MSKCC) who underwent complete surgical resection for adenocarcinoma of the gallbladder were entered and followed continuously in a prospective hepatobiliary database. At MSKCC, gallbladder cancer cases and treatment plans are discussed twice weekly at a multidisciplinary hepatobiliary disease management conference attended by hepatobiliary surgeons, gastroenterologists, medical and radiation oncologists, and diagnostic/interventional radiologists. After histologic review and confirmation of adenocarcinoma or adenosquamous pathology, there were 109 adult patients with confirmed gallbladder cancer who underwent resection. The primary endpoints were disease-specific survival (DSS) and morbidity.

Recorded patient data included clinical characteristics, pathologic findings, and follow-up. Extracted data from the database which computerized patient records for analysis included patient demographics (including age and gender), clinical history, tumor and pathologic characteristics, type of procedure, hospital course including complications, and status at last follow-up. Postoperative follow-up included physical examination with computed tomography or magnetic resonance imaging every 4–6 months. This study was conducted after Institutional Review Board approval.

Definitions

Nomenclature for extent of hepatic resection is defined as follows. Major hepatectomy is defined as right or left hemihepatectomy or extended hepatectomy. Extended right hepatectomy includes resection of Couinaud's segments 4, 5, 6, 7, and 8.[15] Extended left hepatectomy includes resection of segments 2, 3, 4, 5, and 8. Right hemihepatectomy refers to resection of segments 5, 6, 7, and 8, and left hemihepatectomy refers to resection of segments 2, 3, and 4. For the purpose of this study, minor hepatic resection is defined as resection of segments 4B and V or less.

Radiologic and operative data were reviewed for the presence or suspicion of inflow vascular involvement by tumor mandating major hepatectomy. Some patients without evidence of inflow involvement underwent empiric major hepatectomy while others underwent minor hepatectomy. Differences within our group's practice show a trend away from empiric major hepatectomy, which accounts for these different approaches and allows an analysis of the outcome in each situation. Over time, our approach to resection has evolved from empiric major hepatectomy to more limited resection when such resection can completely remove the tumor or gallbladder bed without compromising margins.

Radiology and operative reports were also reviewed for the presence of factors that mandate a resection of the common bile duct. These factors include inability to obtain a negative cystic duct margin, nodal involvement of the porta hepatis adherent to the common bile duct or scar/adhesions involving the common bile duct that could not be differentiated from tumor. Some patients underwent empiric common bile duct excision to enhance the portal lymphadenectomy in the absence of common bile duct involvement. Similarly, differences among our group's practice account for these approaches and allow for analysis of outcomes in each situation. Lymph node dissection consisted of resection of lymphatic tissues in the porta hepatis, porta-caval space, and supraduodenal areas.

Patients who underwent a previous cholecystectomy and were found to have gallbladder cancer confined to the mucosa were typically not recommended for reoperation and resection. Clinical staging of disease was performed by American Joint Committee on Cancer (AJCC) staging.[16]

Morbidity Staging System

All in-hospital deaths were considered surgical mortality. Perioperative complications within 30 days of operation were graded using a previously described

surgical secondary events grading system categorized as follows: grade 1 complication required local or bedside care; grade 2 complication required invasive monitoring or intravenous medication; grade 3 complication required operation, interventional radiology, intubation, or therapeutic endoscopy; grade 4 complication resulted in persistent disability or required major organ resection; and grade 5 complication resulted in death.[17] The highest severity level was recorded when a patient had more than one complication associated with a specific procedure.

Statistical Analysis

Clinicopathologic correlates were analyzed using the chi-square test or Fisher exact test, where appropriate, for univariate comparisons. Means testing of continuous variables was performed with the Student *t*-test. Multivariate analyses were performed via a Cox proportional hazards model. Survival analyses were performed considering pathologic variables (overall stage, T stage, N stage, differentiation, margin status), patient variables (age, gender), and operative variables (prior cholecystectomy, major hepatectomy, common bile duct involvement, common bile duct excision, vascular inflow involvement, and adjacent organ resection). Survival was determined using Kaplan–Meier methodology, and univariate comparisons were made using the log-rank test for categorical variables. Disease-specific survival (DSS) was defined as time from definitive resection to date of death as a result of disease or complication, or last follow-up. Deaths due to other causes were censored. Disease-free survival (DFS) was defined as time from resection to date of first relapse or last follow-up. Analyses were performed using the SPSS statistical package (SPSS, Inc., Chicago, IL). Differences were considered significant at the $p = 0.05$ level.

Results

Clinical and Pathologic Characteristics

Between October 1988 and April 2002, a total of 109 patients underwent evaluation and surgical treatment for adenocarcinoma of the gallbladder. There were five postoperative deaths (5%), leaving 104 evaluable patients for long-term outcome. Median age was 65 (range 28–85) years, and 74 patients were female (71%).

Treatment and pathologic variables are summarized in Table 1 and discussed throughout the text. The majority of patients had undergone a cholecystectomy prior to definitive therapy ($n = 62$, 69%). Ninety-seven patients (93%) underwent portal lymphadenectomy. Most patients did not receive adjuvant therapy. Four patients (4%) underwent adjuvant chemotherapy and 11 patients (11%) adjuvant chemotherapy with radiation. Of the 11 patients who received radiation, 4 had a positive margin as their indication for such treatment.

When analyzed by time periods, there was no change in the performance of bile duct excision or other organ resection comparing the inclusive years from 1988 to 1997 and 1998 to 2003 (data now shown). There was a significant trend comparing these two time periods in terms of performance of major hepatectomy, with 22 of 43 (51%) undergoing major hepatectomy in the early time period and 14 of 61 (23%) in the more recent time period.

Disease-Specific Survival

Median follow-up for the entire cohort was 33 months (range 2–156 months), and was 58 months for survivors. The median DSS for the whole cohort was 33 months and actuarial 5-year survival was 42%. Median DFS was 18 months, and actuarial 5-year DFS was 32%. Clinical status at last follow-up was as follows: no evidence of disease—33 (32%), alive with disease—9 (9%), dead of disease—62 (60%). Twenty-seven patients (26%) are actual 5-year survivors, five of whom had positive lymph nodes at resection.

Extent of Liver Resection and Inflow Vascular Involvement

Overall, 36 patients (35%) underwent major hepatectomy. Of these 36 patients, 21 had vascular inflow involvement mandating major hepatic resection and 15 did not but underwent empiric major hepatectomy (Table 1). Regardless of clinical vascular inflow involvement, major hepatectomy was not significantly associated with the other clinical or pathologic parameters. Clinical vascular inflow involvement mandating major hepatectomy was similarly not associated with clinical or pathologic factors (Table 2).

Presence of vascular inflow involvement or performance of a major hepatectomy was not associated with a change in DSS. Patients who underwent major hepatectomy had median survival of 27 months and predicted 5-year survival of 31%, compared with 45 months and 43% for patients who did not undergo major hepatic resection ($p = 0.10$). Similarly, 5-year survival for patients with inflow involvement (27%) did not differ from those without inflow involvement (43%) ($p = 0.19$). Figure 1a and b presents the Kaplan–Meier disease-specific survival curves for major hepatectomy and inflow vascular involvement, respectively.

Common Bile Duct (CBD) Involvement and Excision

Excision of the CBD was carried out in 68 patients (65%). Clinical involvement of the CBD mandating

TABLE 1 Treatment and pathologic variables for the entire cohort ($n = 104$)

Treatment ($n = 104$)		
Prior cholecystectomy	No	32 (31%)
	Yes	72 (69%)
	Laparoscopic	50 (48%)
	Open	22 (21%)
Extent of hepatectomy	Cholecystectomy	10 (10%)
	Segment 4/5	58 (56%)
	Major hepatectomy	36 (35%)
Inflow involvement	No	83 (80%)
	Yes	21 (20%)
[*]Of 83 without pedicle involvement, 15 (18%) underwent major hepatectomy		
CBD excision	No	36 (35%)
	Yes	68 (65%)
CBD involvement	No	68 (65%)
	Yes	36 (35%)
[*]Of 68 without CBD involvement, 32 (31%) underwent CBD excision		
Other organ resection	No	82 (80%)
	Yes	21 (20%)
	Colon	9
	Partial duodenum	4
	Colon, partial duodenum/stomach	3
	Whipple	2
	Partial duodenum, wedge pancreas	1
	Colon, partial duodenum, wedge pancreas	1
	Portal vein	1
Pathology ($n = 104$)		
Overall stage	1a	3 (3%)
	1b	29 (28%)
	2a	37 (36%)
	2b	33 (32%
	3	2 (2%)
T stage	T1	4 (4%)
	T2	37 (36%)
	T3	61 (59%)
	T4	2 (2%)
N stage	N0	70 (67%)
	N1	34 (33%)
Differentiation	Well/well–moderate	19 (20%)
	Moderate	42 (42%)
	Moderate–poor/poor (*nine missing values)	34 (36%)
Margin status	Negative	93 (91%)
	Positive (*two missing values)	9 (9%)

resection was documented in 36 of these patients. Thirty-two patients did not have suspected or proven involvement of the CBD and underwent an empiric CBD excision as part of their resection (Table 1). Clinical involvement of the CBD was associated with higher T ($p = 0.01$) and overall stage ($p = 0.007$), but not N stage or histologic differentiation. CBD excision, regardless of clinical involvement, was not associated with clinical or pathologic variables, but was significantly associated with prior simple cholecystectomy ($p = 0.003$) (Table 3). There was no difference in nodal counts between those who underwent CBD excision and those who did not (data not shown).

Patients with CBD involvement had median survival of 19 months and predicted 5-year survival of 21%, which was significantly worse when compared with 62 months and 49% for patients without CBD involvement

TABLE 2 Association of major hepatectomy and inflow vascular involvement with clinicopathologic variables

Factor	*n*	Major hepatectomy ($n = 36$), *N* (%)	*p*-value	Inflow involved ($n = 21$), *N* (%)	*p*-value
Age, years					
>60	69	21 (58)		13 (62)	
<60	35	15 (42)	0.21	8 (38)	0.62
Gender					
Female	74	28 (78)		17 (81)	
Male	30	8 (22)	0.28	4 (19)	0.42
T stage					
T1/2	41	11 (31)		5 (24)	
T3/4	63	25 (69)	0.18	16 (76)	0.14
N stage					
N0	70	24 (71)		15 (71)	
N1	34	12 (29)	0.92	6 (29)	0.80
Overall stage					
1a/1b	32	10 (24)		5 (24)	
2a/2b/3	72	26 (76)	0.63	16 (76)	0.60
Differentiation					
Well/well–moderate	19	6 (17)		4 (20)	
Moderate	42	14 (39)		8 (40)	
Poor/moderate–poor	34	15 (42)	0.54	8 (40)	0.89
Margin					
Negative	93	34 (94)		19 (91)	
Positive	9	2 (6)	0.40	2 (9)	1.0
Prior chole[a]					
Yes	72	27 (75)		13 (62)	
No	32	9 (25)	0.35	8 (38)	0.16

[a] Limited to the 94 cases treated by more extensive hepatectomy than simple cholecystectomy

($p = 0.01$). CBD excision had no statistically significant impact on DSS ($p = 0.12$). However, there was a trend towards worse survival in patients who underwent CBD excision. Figure 1c and d presents the Kaplan–Meier disease-specific survival curves for CBD involvement and CBD excision, respectively.

Adjacent Organ Resection

Twenty-one patients underwent en bloc resection of adjacent organs, as detailed in Table 1. Fourteen of these cases were performed for a single organ (colon, duodenum or portal vein) while the other seven cases were multi-organ resections. One patient underwent a combined segment 4/5 resection along with a pancreaticoduodenectomy for retropancreatic lymph node metastases. All other resections of adjacent organs were performed for adhesions to the involved organ that could not be distinguished from malignant involvement. Of the 20 cases performed for presumed malignant adhesions, the resected adjacent organ was histologically involved in 10 (50%). Adjacent organ resection was significantly associated with advanced T stage (90% T3 or T4; $p = 0.002$), but not with nodal stage or differentiation ($p =$ not significant). Because of the association with T stage, adjacent organ resection was also associated with higher overall stage ($p = 0.003$). Of the 21 cases that required adjacent organ resection: 15 cases were of T3/4 N0, 4 cases were of T3/4 N1, and there was 1 case each of T2N0 and T1N1.

Performance of adjacent organ resection was not significantly associated with long-term survival. Patients who underwent adjacent organ resection had a trend towards worse survival with median survival of 22 months and predicted 5-year survival of 20%, compared with 40 months and 43% for patients without adjacent organ resection ($p = 0.24$). Figure 1e shows the Kaplan–Meier disease-specific survival curve for adjacent organ resection.

Multivariate Analysis of Disease-Specific Survival

Table 4 summarizes the overall univariate analysis of clinicopathologic factors and their association with disease-specific survival. The statistically significant predictors of poor outcome, exclusive of extent of resection, were advanced T stage ($p = 0.0001$), N stage ($p = 0.0002$), overall stage ($p < 0.0001$), and histologic

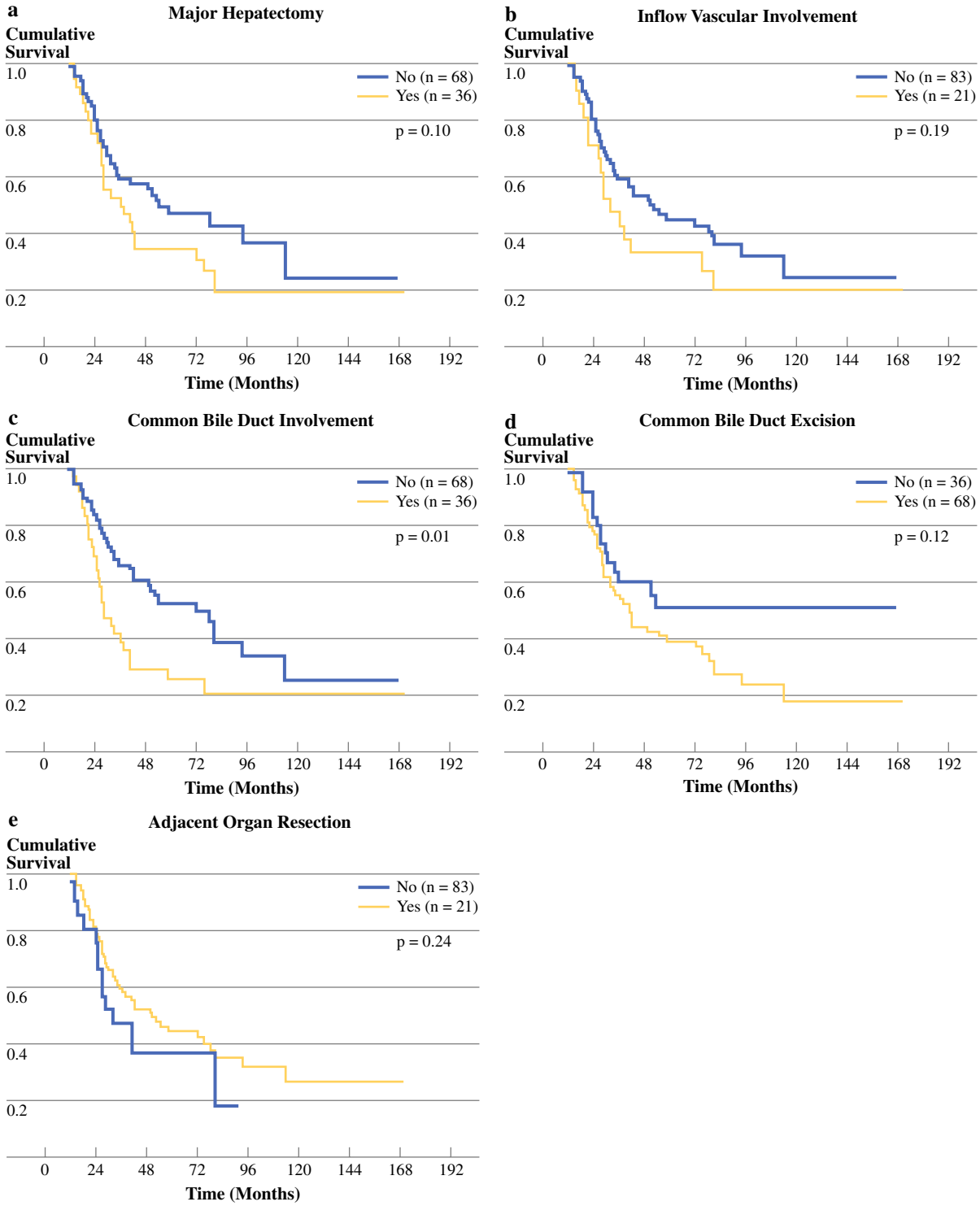

FIG. 1 Disease-specific survival for 104 patients with gallbladder adenocarcinoma treated at Memorial Sloan-Kettering Cancer Center by resection stratified by **a** major hepatectomy, **b** vascular involvement, **c** common bile duct involvement, **d** common bile duct excision, and **e** adjacent organ resection

differentiation ($p < 0.0001$). As noted above, the only factor related to extent of resection that was significantly associated with worse long-term survival was CBD involvement ($p = 0.01$). Figure 2a, b, and c shows the Kaplan–Meier disease-specific survival curves stratified by T stage, N stage, and differentiation.

TABLE 3 Association of common bile duct (CBD) involvement and CBD excision with clinicopathologic variables

Factor	*n*	CBD involved ($n = 36$), *n* (%)	*p*-value	CBD excised ($n = 68$), *N* (%)	*p*-value
Age, years					
> 60	69	26 (72)		47 (69)	
< 60	35	10 (28)	0.39	21 (31)	0.51
Gender					
Female	74	29 (81)		49 (72)	
Male	30	7 (19)	0.17	19 (28)	0.82
T stage					
T1/2	**41**	**8 (22)**		25 (37)	
T3/4	**63**	**28 (78)**	**0.01**	43 (63)	0.53
N stage					
N0	70	21 (58)		45 (66)	
N1	34	15 (42)	0.19	23 (34)	0.83
Overall stage					
1a/1b	**32**	**5 (14)**		20 (29)	
2a/2b/3	**72**	**31 (86)**	**0.007**	48 (71)	0.82
Differentiation					
Well/well–moderate	19	7 (21)		12 (18)	
Moderate	42	15 (44)		31 (46)	
Poor/moderate–poor	34	12 (35)	0.99	22 (32)	0.27
Margin					
Negative	93	33 (92)		63 (93)	
Positive	9	3 (8)	1.0	5 (7)	0.11
Prior chole					
Yes	72	23 (64)		**54 (79)**	
No	32	13 (36)	0.5	**14 (21)**	**0.003**

Bold entries were the statistically significant ones

Multivariate analysis of clinicopathologic factors demonstrated that higher T stage [$p = 0.05$, 95% confidence intervals (CI) 0.99–5.02], higher N-stage ($p = 0.01$, 95% CI 1.10–3.59), poor differentiation ($p < 0.0001$, 95% CI 1.70–3.98), and CBD involvement ($p = 0.02$, 95% CI 0.30–0.90) were independent predictors of worse DSS.

Morbidity and Mortality

Postoperative mortality occurred in 5 of 109 patients (5%), and all of these deaths were in patients who had undergone major hepatectomy and bile duct excision ($p = 0.006$). Three of the postoperative deaths were directly related to intra-abdominal sepsis resulting in multiorgan failure. Liver and renal failure was responsible in the other two mortalities. Overall, perioperative morbidity was 53%. Of the 51 patients who had postoperative complications, 12 (23%) were considered grade 1, 13 (25%) grade 2, 25 (49%) grade 3, and 1 (2%) grade 4. The 29 specific grade 3 and 4 complications which occurred in 26 patients were 14 abscesses, 6 biliary fistulae, 2 respiratory failures, 2 serous fluid collections, 1 gastric outlet obstruction, and 4 other cardiopulmonary complications. Table 5 summarizes the associations of the demographic, staging, and operative variables with perioperative morbidity. The only significant associations with worse perioperative outcome were with performance of major hepatectomy ($p = 0.009$) and bile duct excision with hepaticojejunostomy reconstruction ($p = 0.03$). Of the 66 patients who underwent CBD excision and hepaticojejunostomy, there were 19 (29%) cases of abscess and/or biliary fistulae requiring percutaneous drainage.

DISCUSSION

Overall survival for all patients with gallbladder cancer is dismal, and nihilism regarding the surgical treatment of this disease was prominent until the last few decades. Despite improvements in outcome associated with extended resections involving a hepatectomy and regional lymph nodes, no consensus regarding the appropriate extent of resection has been established. Interestingly, as far back as the 1950s, Glenn and Hays proposed a rational approach, which included wedge resection of the liver involving the gallbladder fossa as well as a regional lymphadenectomy of the hepatoduodenal ligament.[18] However, there remains a wide

TABLE 4 Overall analysis of prognostic factors associated with disease-specific survival

Factor	*n*	Median survival (months)	Five-year survival (%)	*p*-value
Age, years				
>60	69	33	39	
<60	35	43	41	0.54
Gender				
Female	74	43	46	
Male	39	27	25	0.14
Time period				
1988–1997	43	29	41	
1998–2003	61	33	25	0.2
T stage				
T1/2	**41**	**103**	**64**	
T3/4	**63**	**24**	**25**	**0.0001**
N stage				
N0	**70**	**65**	**51**	
N1	**34**	**18**	**17**	**0.0002**
Overall stage				
1a/1b	**32**	**103**	**74**	
2a/2b/3	**72**	**22**	**26**	**<0.0001**
Differentiation				
Well/well–moderate	**19**	**NR**	**62**	
Moderate	**42**	**68**	**49**	
Poor/moderate–poor	**34**	**18**	**15**	**<0.0001**
Margin				
Negative	93	40	45	
Positive	9	16	17	0.25
Prior chole[a]				
Yes	70	44	44	
No	24	26	29	0.37
Major hepatectomy				
No	68	45	43	
Yes	36	27	31	0.10
Pedicle involvement				
No	83	43	43	
Yes	21	22	27	0.19
CBD involvement				
No	**68**	**62**	**50**	
Yes	**36**	**19**	**20**	**0.01**
CBD excision				
No	36	NR	50	
Yes	68	31	37	0.12
Adjacent organ resection				
No	83	40	43	
Yes	21	22	20	0.24

NR not reached

[a] Limited to the 94 cases treated by more extensive hepatectomy than simple cholecystectomy

Bold entries were the statistically significant ones

variety in what is considered the best surgical approach for gallbladder cancer. In 1991, 49% of surveyed surgeons recommended lymphadenectomy and 64% recommended liver resection.[19] Recommendations have ranged from simple cholecystectomy to aggressive resections including major hepatectomy, lymphadenectomy, and even combined hepatecto-pancreaticoduodenectomy.[20]

There are two major issues that must be addressed when considering the optimal operation for gallbladder cancer, namely the extent of hepatic resection and the extent of the

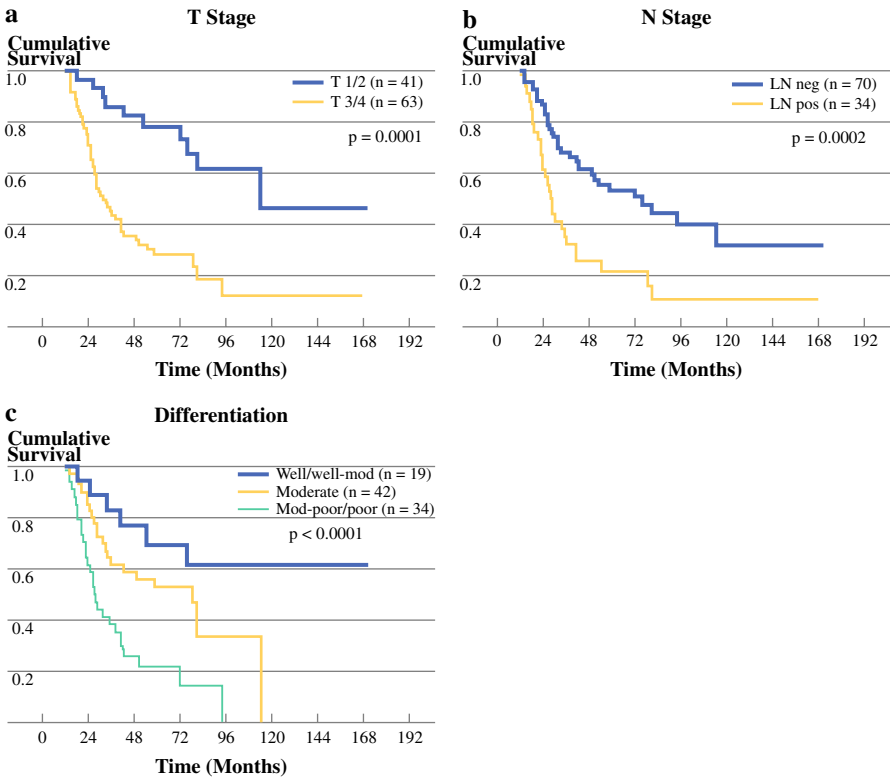

FIG. 2 Disease-specific survival for 104 patients with gallbladder adenocarcinoma treated at Memorial Sloan-Kettering Cancer Center by resection stratified by **a** T stage (1/2 and 3/4), **b** N status, and **c** differentiation (well/well to moderately differentiated, moderately differentiated, moderate to poorly/poorly differentiated)

regional lymphadenectomy. A simple cholecystectomy invades the subserosal plane in dissecting the gallbladder off the cystic plate of the liver and, therefore, will most likely result in an involved margin if the tumor approximates or invades through the thin muscular wall of the gallbladder wall. In a review by Yamaguchi and Tsuneyoshi, of 25 patients who had tumor extending into the subserosal layer, 11 patients had positive microscopic margins after simple cholecystectomy.[21] This has led to the concept that resection of the liver tissue around the gallbladder fossa is necessary to ensure a complete resection of all malignant tissue in this area. Second, gallbladder cancer has a strong propensity to metastasize to regional lymph nodes. In fact, regional nodal metastases may be as high as 43% for T2 tumors alone.[22] Early spread generally involves the cystic duct node and choledochal nodes; however, early spread to celiac, retropancreatic, and aortocaval nodes is relatively common. Nodal spread beyond the hepatoduodenal ligament (celiac, retropancreatic, aortocaval) generally represents metastatic disease and precludes a curative operation. Therefore, after assessment of distant lymph nodes, a lymphadenectomy including all nodal tissue in the hepatoduodenal ligament, has become an integral part of these operations.[9] Since this was performed in over 90% of our patients, we could not include this in our analysis.

The extent of operation necessary to treat gallbladder cancer has a wide range and depends on the depth of tumor penetration, location of the tumor, involvement of the inflow vascular pedicle or CBD, adherence to adjacent organs, and the bias of the treating surgeon. The extent of hepatectomy necessary to achieve adequate clearance of malignant tissue, while minimizing morbidity, remains unknown. For tumors confined to the mucosa and not invasive of the muscularis layer (T1a), simple cholecystectomy is associated with a 90–100% cure rate.[7,23] For T2 cancers, simple cholecystectomy is associated with 5-year DSS of 24–40%, whereas cholecystectomy combined with liver resection and regional lymphadenectomy is associated with a greater than 80% long-term survival rate.[7,9,21,22,24,25] The treatment of T3 and T4 tumors has been more controversial as these tumors tend to be more invasive and require more extensive resections, which previously have not resulted in improved long-term survival with the exception of node-negative tumors.[1,2,26]

This study was undertaken to analyze the extent of hepatic resection, common bile duct (CBD) excision, and adjacent organ resection for gallbladder adenocarcinoma, and to ascertain its association with disease-specific survival (DSS) and perioperative morbidity. Many patients in this study were included in a previous overall analysis of gallbladder cancer from our institution, but the current study differed significantly in that we included only patients with adenocarcinoma and performed a very specific analysis of the extent of resection which was not analyzed in the previous study.[3] This study was possible since over the

TABLE 5 Associations of clinicopathologic factors with perioperative morbidity

Morbidity grade					
Factor	n[a]	0 (%)	1/2 (%)	3/4 (%)	p-value
Age, years					
>60	67	33 (49)	14 (21)	20 (30)	
<60	29	12 (41)	11 (38)	6 (21)	0.21
Gender					
Female	69	35 (51)	19 (28)	15 (22)	
Male	27	19 (37)	6 (22)	11 (41)	0.17
T stage					
T1/2	36	21 (58)	9 (25)	6 (17)	
T3/4	60	24 (40)	16 (27)	20 (33)	0.14
N stage					
N0	65	31 (48)	16 (25)	18 (28)	
N1	31	14 (45)	9 (29)	8 (26)	0.90
Overall stage					
1a/1b	28	16 (57)	6 (21)	6 (21)	
2a/2b/3	68	29 (43)	19 (28)	20 (29)	0.43
Prior cholecystectomy					
Yes	68	35 (52)	17 (25)	16 (24)	
No	28	10 (36)	8 (29)	10 (36)	0.33
Major hepatectomy					
No	**62**	**36 (58)**	**14 (23)**	**12 (19)**	
Yes	**34**	**9 (27)**	**11 (32)**	**14 (41)**	**0.009**
Bile duct excision					
No	**30**	**20 (67)**	**6 (20)**	**4 (13)**	
Yes	**66**	**25 (38)**	**19 (29)**	**22 (33)**	**0.03**
Adjacent organ resection					
No	76	38 (50)	19 (25)	19 (25)	
Yes	20	7 (35)	6 (30)	7 (35)	0.47

[a] The n values do not add up to 104 because complete data was only available for 96

Bold entries were the statistically significant ones

12-year period during which this study spans, both our service's overall attitude toward resection for gallbladder cancer as well as the differences among approaches by the various surgeons within the hepatobiliary surgical team have varied. There was a clear and statistically significant trend away from major hepatic resections, although the use of bile duct excision and adjacent organ resection did not change over time. Importantly, disease-specific survival did not significantly change over time.

This study demonstrates that significant independent predictors of survival were advanced overall T and N stage and histologic differentiation. Major hepatectomy, with or without inflow vascular involvement, was not significantly associated with differences in survival. This is likely due to the fact that both the performance of a major hepatectomy and vascular inflow involvement were not significantly associated with differences in staging parameters that affect survival the most. Therefore, it is most likely that tumor biology and tumor stage, rather than tumor location or extent of hepatectomy, determine long-term outcome.

This study also demonstrates that CBD involvement was associated with advanced T stage and a trend towards advanced N stage. With these associations in mind it is not surprising that CBD involvement was also associated with worse survival. Interestingly, on multivariate analysis, CBD involvement retained an independent association with survival, implying that this finding is an important marker of advanced disease. On the other hand, CBD excision, regardless of CBD involvement, was not associated with staging parameters or survival, although there was a trend towards worse survival with CBD excision. This is not surprising since CBD involvement was a major predictor of outcome and populated the CBD excision group exclusively. Overall, this further supports the notion that tumor biology and stage are the most important determinants of outcome, rather than extent of resection.

In this series, adjacent organs were resected in 21 patients. With one exception, resection of adjacent organs was performed for adhesions to the involved organ that could not be distinguished from malignant involvement. Of the 20 cases performed for presumed malignant adhesions, the resected adjacent organ was histologically involved in half of the cases, emphasizing the importance of resecting any suspicious adherent organ. Not surprisingly, adjacent organ resection was significantly associated with advanced T stage (90% T3 or T4), but interestingly not with nodal stage. It is important to note that, of the 21 cases that required adjacent organ resection, 16 were node negative, emphasizing that the finding of adherent organs does not necessarily imply advanced disease. This is also supported by the finding that adjacent organ resection was not associated with changes in DSS. Most importantly, adjacent organ resection can be performed safely in experienced hands with no demonstrable increase in perioperative morbidity.

The overall morbidity and mortality rates in this series of 53% and 5% are consistent with previously reported rates of 5–54% and 0–21%, respectively.[5,6,20] We find these figures acceptable in the face of very challenging operations that are often performed as a reoperation for a disease that, when unresected, has 5-month median survival. Furthermore, half of the complications were grade 1 or 2. Major hepatectomy and CBD excision with hepaticojejunostomy reconstruction were the only factors associated with higher morbidity and a combination of the two accounted for all five postoperative deaths. This is not surprising, as biliary reconstruction and the extent of liver resection are well-known predictors of morbidity after partial hepatectomy. Biliary reconstruction in these cases is often performed with hepaticojejunostomy to a small

proximal bile duct, accounting for a higher risk of bile leakage and/or abscess.

This study must be interpreted with some caution. While the majority of operative and pathologic data have been recorded prospectively, the retrospective review of operative reports and radiology findings to determine the necessity of major hepatic resection or common bile duct resection is somewhat subjective. Furthermore, limited numbers in the groups of patients we analyzed certainly increases the risk of false findings. On the other hand, the rarity of gallbladder cancer limits the ability to perform prospective, randomized studies or even large retrospective analyses and it is therefore incumbent on surgeons to continue to reanalyze outcomes related to such therapy. Importantly, the time period itself, which may be reflective of better imaging and staging, did not impact changes in outcome in this analysis.

In conclusion, this study provides evidence that tumor biology and stage, not extent of resection, is the most important predictor of outcome after resection for gallbladder cancer. The goals of definitive resection should therefore be cholecystectomy with en bloc resection of invaded organs (most commonly the liver) around the tumor to provide reasonable margins and to resect regional lymph nodes. Since major hepatic and biliary resections increase morbidity and do not appear to improve outcome, they should only be performed when necessary to clear all disease. Resection of segment IVb and V should be adequate hepatic resection in the majority of cases of T1b or greater cancers. Major resections should be performed in medically fit patients with localized but poorly placed tumors involving inflow vascular structures, as resection is still associated with long-term survival in these situations. Biliary resections are not mandatory and should only be performed when feasible and necessary to clear locally invasive tumors or adherent nodal disease.

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