ANNALS OF SURGERY
Vol. 224, No. 5, 639–646

Long-Term Results After Resection for Gallbladder Cancer

Implications for Staging and Management

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Background
The surgical management of gallbladder cancer is controversial. There is no consensus among surgeons as to the indications for reoperation or radical resection.

Objective
The purpose of this study was to examine results of reoperation after an incidental finding of gallbladder cancer after cholecystectomy, and results of radical resection in patients with advanced disease.

Methods
A retrospective review of 149 patients with the diagnosis of gallbladder cancer treated from 1985 to 1993 was performed. Fifty-eight patients were explored and 23 underwent resection for cure. Resection included trisegmentectomy in nine patients and bile duct resection in ten patients. Seventeen patients underwent re-exploration after an incidental finding of gallbladder cancer at initial cholecystectomy.

Results
Surgical resection is associated with an actuarial 51% 5-year disease-free survival rate, with a median follow-up time of 48 months. Eight patients are alive beyond 50 months. There were no operative deaths; the perioperative morbidity rate was 26%. Nodal status is the most powerful predictor of outcome. Two patients with T4, N0 disease are alive without evidence of disease beyond 4 years. Thirteen of the 17 patients (76%) undergoing reoperation after simple cholecystectomy for T2 or T3 tumors had residual disease.

Conclusions
Patients with nodal metastasis beyond the pericholedochal nodes should not be considered for curative resection. Tumors staged T4, N0 should be included with stage III disease, and resection should be considered. Re-resection of T2 or T3 tumors after simple cholecystectomy is likely to include residual disease and should thus provide the only chance for long-term survival.

The 5-year survival rate of patients with gallbladder cancer is dismal; it is less than 5% in most large series, with a median survival of less than 6 months.[1,2] The surgical management of gallbladder cancer is controversial, with surgeons recommending operations ranging from simple cholecystectomy to combined extended hepatectomy and common bile duct resection for the same stage disease. Some studies have indicated that long-term survival is achievable with radical resection, even in advanced-stage disease,[3] but there is no consensus as to the indications for radical resection. A recent survey of prominent gastrointestinal surgeons in the United States indicated that 49% recommended lymph node dissection and 64% recommended some form of liver resection for stages T2–T4 disease. Twenty-one percent recommended simple cholecystectomy alone for node-positive disease.[4] Likewise, many authors recommend re-exploration and radical resection after cholecystectomy for early-stage disease,[5] but the benefit of such an approach remains unproven.

The rarity of gallbladder cancer limits the ability to perform prospective, randomized studies of therapy, and the majority of cases present at an unresectable stage. For example, 69% of gallbladder cancers recorded in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute presented with adjacent organ invasion or distant metastasis.[6] Despite these limitations, surgical resection has been the only form of therapy that has impacted on the natural history of gallbladder cancer.[7]

The most pertinent questions are whether re-resection is indicated for incidental T2 or T3 tumors discovered at histologic examination after simple cholecystectomy, and whether any operation is indicated in patients with > 2cm liver invasion (T4). The purpose of this study is to provide follow-up of patients with gallbladder cancer treated by radical resection. Included for analysis are patients re-resected after an incidental finding of gallbladder cancer at cholecystectomy and those undergoing extended resections for advanced disease at presentation. Patterns of recurrence and long-term survival taken in the context of morbidity data allow assessment of the indications for radical surgery.

METHODS

Patients seen at Memorial Sloan-Kettering Cancer Center from 1985 to 1993 with the diagnosis of gallbladder cancer were identified from admission diagnosis data, the tumor registry, and a prospective hepatobiliary database. Data collected from chart review, office visits, and a telephone questionnaire included patient demographics, laboratory data, operative management, surgical morbidity, length of hospital stay, pathologic findings, and long-term follow-up.

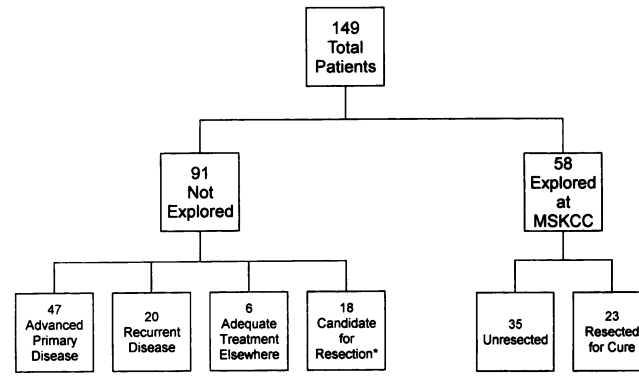

Figure 1. Management of all patients presenting with gallbladder cancer. *Good candidates for resection, but not operated because of medical problems or physician preference.

One hundred forty-nine patients were seen with the diagnosis of gallbladder cancer. Median age was 61 years (range, 28–84 years). There were 99 women and 50 men. Histologic examination revealed adenocarcinoma in 137 patients (92%), adenosquamous tumors in 5, squamous carcinoma in 4, carcinoid in 2, and spindle cell sarcoma in 1 patient.

The most common presenting symptom was biliary colic in 59% (88 of 149 patients), followed by jaundice in 28% and weight loss in 9%. Forty-two percent of patients had biliary tract cancer suspected preoperatively. Sixty percent of patients (90/149) had stage IV disease, 25% had stage III, and 13% had stage II. Ninety-four percent of tumors were associated with gallstones. Of the 149 patients, 91 were not subjected to surgery at Memorial Sloan-Kettering Cancer Center (Fig. 1). Of the 58 patients explored for resection, 53 had adenocarcinoma, 2 had adenosquamous tumors, 1 had squamous carcinoma, and 2 had carcinoid tumors. Three patients had papillary tumors, whereas the remainder had tumors that were infiltrative in nature. Only six patients had well-differentiated tumors.

Thirty-five of the 58 patients subjected to operation had tumors that were unresectable for cure (Fig. 1). Reasons for unresectability included extensive local involvement in 7 (20%), discontinuous liver metastasis in 12 (34%), peritoneal implants in 13 (37%), and bulky nodal metastasis in 9 (26%). Six patients had involvement of more than one site, preventing resection. Of the 20 patients explored for resection who presented with jaundice, only 4 were resectable for cure.

Twenty-three patients (40% of explored patients) un-

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Accepted for publication August 29, 1995.

Table 1. STAGING FOR GALLBLADDER CANCER

Stage	TNM[9]	Modified Nevin[22,29,30]	Recommended Revised Staging
I	Mucosal or muscular invasion (T1N0M0)	*In situ* carcinoma	Mucosal or muscular invasion
II	Transmural invasion (T2N0M0)	Mucosal or muscular invasion	Transmural invasion
III	Liver invasion <2 cm; lymph node metastasis (T3N1M0)	Transmural direct liver invasion	(A) liver invasion <2 cm (T3N0M0) (B) liver invasion >2 cm; N1 disease (T4N0M0, TxN1M0)
IV	(A) liver invasion >2 cm (T4N0M0, TxN1M0) (B) distant metastasis (TxN2M0, TxNxM1)	Lymph node metastasis	Distant metastasis (TxN2M0, TxNxM1)
V	—	Distant metastasis	—

derwent curative resection. This group consists of 8 men and 15 women, with a median age of 58 years (range, 38–78 years). The resection procedure consisted of a hepatic wedge resection or segmentectomy in 11 patients, lobectomy in 3, and trisegmentectomy in 9. Ten of the 23 patients with hepatic resection had a common bile duct resection and reconstruction.

The median follow-up time was 48 months, ranging from 4.2 to 120 months. The tumors were staged as per the TNM classification (International Union Against Cancer [UICC]/American Joint Committee on Cancer [AJCC]; Table 1).[8,9] All patients had at least T2 disease. Survival was calculated and plots constructed by the Kaplan-Meier method. A Cox univariate and multivariate analysis was performed to determine prognostic factors for survival.

RESULTS

Survival

The median survival for the 35 patients with unresectable tumors was 5.2 months, with only 1 patient alive beyond 2 years. For those resected, the 5-year actuarial overall survival rate was 58% (Fig. 2). Disease has recurred in 9 of 23 patients. The initial site of recurrence was local liver in two patients, distant nodal disease in two patients, peritoneal seeding in four patients, and lung metastases in one patient. Actuarial 5-year survival rates are 83% for stage II, 63% for stage III, and 25% for stage IV. Two of seven patients with stage IV (T4, N0) disease are alive without disease beyond 4 years (Fig. 3).

Seventeen patients were re-explored, with an incidental finding of gallbladder cancer after cholecystectomy (Table 2). Five of these patients (29%) had unresectable tumors. Twelve patients had resectable disease, for which the overall 5-year survival rate was 41%. This includes three patients with M1 disease that was presumed to be secondary to dissemination at the time of cholecystectomy. The 5-year survival rate of the nine patients without M1 disease was 63%. Thirteen patients (76%) had pathologically detectable residual disease at the time of re-exploration.

Thirteen patients underwent laparoscopic evaluation

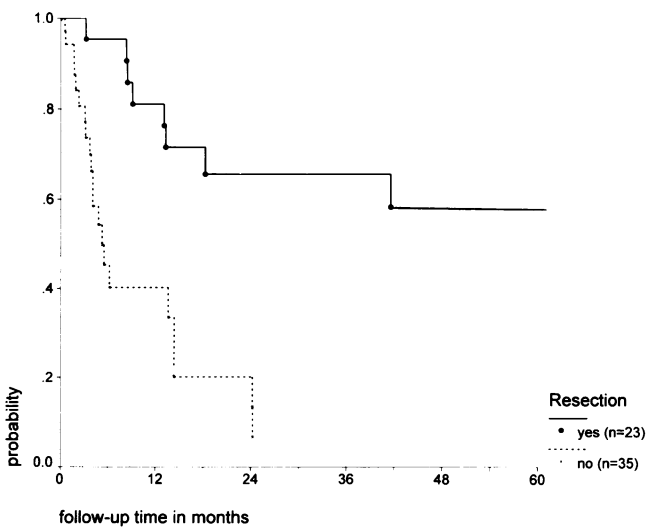

Figure 2. Kaplan-Meier survival by resectability. $p < 0.05$ by log rank.

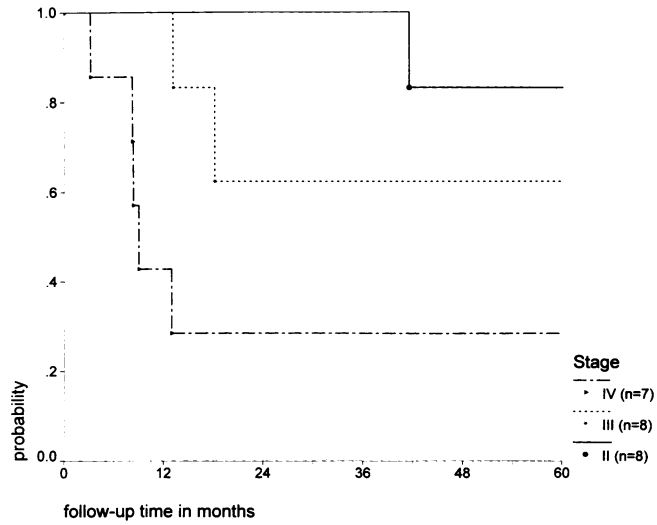

Figure 3. Kaplan-Meier survival by stage. $p < 0.05$ by log rank.

Table 2. PROCEDURE, FINDINGS, AND RESULTS OF RERESECTION FOR GALLBLADDER CANCER DISCOVERED INCIDENTALLY AT CHOLECYSTECTOMY

Patient No.	T Stage	2nd Procedure	Findings	Follow-up
1*	3	Exploratory laparotomy/unresectable	Peritoneal seeding	DOD at 5 mo
2*	2	Hepatic wedge/CBD resection	Umbilical port site seeding (resected)	AWD at 16.5 mo
3	2	Exploratory laparotomy/unresectable	Bulky portal nodes	AWD at 12 mo
4	2	Hepatic wedge/LND	No residual disease	DOC at 57 mo
5	3	Hepatic wedge/LND	No residual disease	DOD at 41 mo
6	2	Hepatic lobectomy/LND	No residual disease	NED at 56 mo
7*	3	Hepatic wedge/LND	Residual disease in GB bed and lymph nodes	NED at 10 mo
8*	2	Exploratory laparotomy/unresectable	Bulky portal nodes	AWD at 6 mo
9*	2	Trisegmentectomy/CBD resection	No residual disease	NED at 18 mo
10*	2	Hepatic wedge/LND	Residual nodal disease	DOD at 18 mo
11	3	Exploratory laparotomy/unresectable	Distant liver metastasis	DOD at 5 mo
12	3	Exploratory laparotomy/unresectable	Peritoneal seeding	DOD at 11 mo
13	2	Trisegmentectomy/CBD resection	Residual nodal disease	DOD at 13 mo
14	NA	Hepatic lobectomy/Whipple	Peritoneal seeding (resected)	DOD at 13 mo
15	3	Trisegmentectomy/LND	Residual disease in GB bed	DOC at 64 mo
16	3	Trisegmentectomy/CBD resection	Residual disease in GB bed	NED at 31 mo
17*	3	Trisegmentectomy/CBD resection	Peritoneal seeding (resected)	DOD at 3 mo

CBD = common bile duct; LND = lymph node dissection; GB = gallbladder; DOD = dead of disease; AWD = alive with disease; NED = no evidence of disease; DOC = died of other causes; NA = not applicable.
* Initial laparoscopic cholecystectomy.

as their initial procedure, and seven of these underwent laparoscopic cholecystectomy, with an incidental finding of gallbladder cancer (Table 2). Three of the seven patients had peritoneal seeding at the time of their reexploration—one at the umbilical port site.

Four patients received postoperative adjuvant therapy after complete resection. Three patients received combined chemotherapy and radiotherapy, and one patient received postoperative chemotherapy alone. Three of the four patients have died of their disease at 3, 8, and 13 months, respectively. One patient is without evidence of disease at 10 months.

Table 3 provides a breakdown of pathologic findings, resectability, and survival by T stage for the 58 patients explored for resection. Although there is a trend toward increasing incidence of nodal disease with increased T stage, there are six patients with T2 disease having nodal metastasis, and three patients with T4 primary tumors and no nodal metastasis. Overall, 26 patients had distant metastasis at the time of exploration for cure. The most common site was peritoneal seeding or wound implantation in 15 patients (58%).

The results of univariate and multivariate analyses for predictors of survival are summarized in Table 4. Only nodal status is a significant predictor of survival in multivariate analysis. The 5-year survival rate of patients with N0 disease is 81% (Fig. 4). Three of the four patients resected who presented with jaundice underwent common bile duct resection. Only one of these four patients has survived beyond 18 months.

Of the six patients with well-differentiated tumors, four had N2 nodal disease. Four were resectable for cure, and two (N0) were long-term survivors. Although tumor differentiation is not a significant predictor of survival after resection, the morphologic variant may be important. Two of the three patients with papillary tumors are long-term survivors. Three patients underwent curative resections that included resection of M1 disease. All three had presumed implantation of tumor as a result of previous surgery. Two are dead of disease at 8 and 13 months, respectively, and the third is alive with recurrence at 13.5 months.

Morbidity and Mortality

There were no operative deaths, and the overall morbidity rate was 26%. The complication rate was highest for those undergoing a common bile duct resection (Table 5). Only two patients required reoperation, and four required a percutaneous procedure for drainage of a biliary collection or abscess. The median hospital stay was 11.5 days.

DISCUSSION

Gallbladder cancer carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. The extent of resection for each stage of disease is controversial. Most

Table 3. PATHOLOGIC FINDINGS, RESECTABILITY, AND SURVIVAL BY T STAGE

T Stage	No.	N+	M-1	Resectable	5-yr Survival†
2	13	6	0	10 (77%)	69
3	13	7	6	6 (46%)	67
4	30	27	18	6 (20%)	33
Total	58*	40	26	23 (40%)	51

* Two patients with undefined T stage.
† Five-year disease free survival after curative resection.

surgeons agree that T1 disease does not require any operation other than simple cholecystectomy. The prognosis is good, and the morbidity of more radical surgery is not justified.[10] We have shown that in T2 disease, the incidence of lymph node metastasis is 46%, and five of eight patients had residual disease in the lymph nodes or peritoneal seeding after simple cholecystectomy, suggesting that simple cholecystectomy is not adequate. In addition, with radical resection, the 5-year survival rate is 69% for T2 disease. This compares favorably to the best results for simple cholecystectomy, a 5-year survival rate of 40% being reported.[5]

Similarly, in T3 disease, the incidence of nodal disease is 54%, and seven of eight patients had residual disease on re-resection after simple cholecystectomy, suggesting that simple cholecystectomy alone is inadequate. The 5-year survival rate is 67% in this study after complete resection. Although there is no group undergoing observation alone for comparison, it is certain that residual disease would lead to recurrence and death within 3 years.[11]

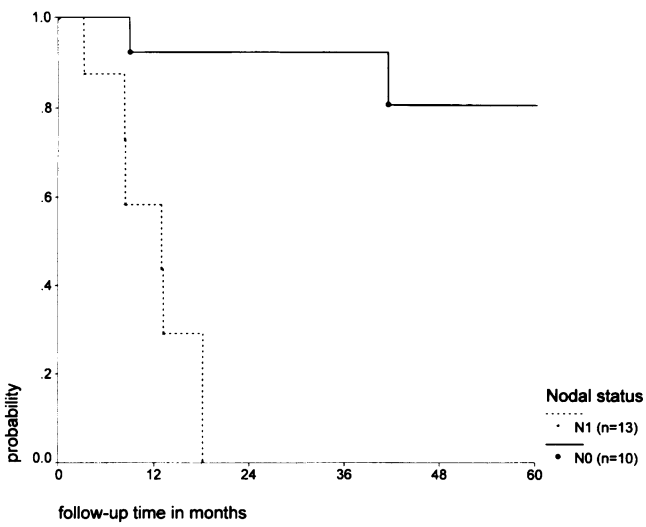

Figure 4. Kaplan-Meier survival by nodal status. $p < 0.05$ by log rank.

Table 4. P VALUES FOR COX REGRESSION ANALYSIS OF VARIABLES AS PROGNOSTIC INDICATORS FOR SURVIVAL AFTER COMPLETE RESECTION

Variable	Univariate Significance	Multivariate Significance
T stage	0.02	0.33
N stage	0.002	0.04
M stage	0.03	0.07
H stage	0.009	0.17
B stage	0.04	0.23
Overall stage	0.01	0.12
Differentiation	0.1	
Total bilirubin	0.19	
Albumin	0.1	
Alkaline phosphatase	0.11	
Age	0.9	
Initial laparoscopy	0.9	

H = level of hepatic involvement; B = level of bile duct involvement.

The issue in T4 disease is somewhat different. Conventional clinical judgment is that the prognosis is poor, regardless of treatment, and that the morbidity of resection is not justified. Nevertheless, the current study provides evidence that complete surgical resection of bulky local disease can lead to long-term survival in two of seven patients, and that this can be accomplished with no treatment-related mortality. The long-term survivors have T4, N0 tumors, suggesting that resection is justified if there is no gross nodal involvement at the time of operation.

Jaundiced patients also require special consideration because they are less likely to have resectable tumors and

Table 5. TREATMENT MORBIDITY BY PROCEDURE

Procedure	N	Morbidity	Mortality	Median Hospital Stay (days)
Limited hepatic resection*	11	1	0	10
Hepatic lobectomy	3	2	0	21
Hepatic trisegmentectomy	9	3	0	21.5
Hepatic resection and CBD resection	10	5	0	23.5
Total	23	6	0	11.5

CBD = common bile duct.
* Hepatic wedge; segment IVb, V resection.

more likely to have a major complication after liver resection.[12] In addition, resection of the bile duct is required in the majority of patients presenting with jaundice, which also increases the morbidity of the procedure. Endoscopic retrograde cholangiopancreatography may be helpful in determining the etiology of ductal obstruction and defining the extent of ductal involvement by tumor. Only selected cases should be considered for curative resection.

The ominous finding of no long-term survivors with node-positive disease is in contrast to studies that have documented long-term survivors with nodal metastases.[5,13–15] Three of ten patients in the current study still are without evidence of disease after resection of nodal metastasis (< 18 months follow-up to date). Other studies have reported 100% recurrence after resection of nodal disease.[3,16–20] Shirai reported ten long-term survivors with nodal metastasis to the region of the cystic and common bile ducts (N1).[21] It may be that patients with retroportal, peripancreatic, or celiac nodal disease (N2) are not worth resecting, given the poor outcome.

The current AJCC staging system includes T2 or T3, N1 disease as stage III, whereas T4, N0 disease is stage IV. In our series, two of three patients with T4, N0 disease are alive more than 4 years after resection, whereas no patient with nodal disease is alive beyond 18 months. The presence of nodal metastasis may indicate a more aggressive biology than a tumor that locally invades the liver. A modified Nevin staging system is more predictive of survival, but lacks the differentiation between T2 and T3 tumors (Table 1).[22] We suggest a modification of the AJCC system, classifying T4, N0 and TX, N1 tumors as stage IIIB, and TX, N2 tumors as stage IV disease (Table 1).

Radical resection that includes resection of peritoneal and wound seeding secondary to contamination at previous surgery or biopsy is controversial. Some have advocated resection of M1 disease presenting as discontinuous liver metastases when it can be encompassed in the resection specimen.[14] Advocates of such aggressive resection see peritoneal spread not so much a reflection of dissemination and aggressive biology, but rather an error in prior operative technique. In the current study, three patients underwent resection of grossly apparent abdominal wall or peritoneal implants as part of a curative radical resection, and disease has recurred in all within 16 months. Further study is required for definitive conclusions in this regard.

Morbidity and mortality of major liver resections has decreased in recent reports, even in the older population.[23,24] This allows for more aggressive management of gallbladder cancer. Major morbidity rates after resection for gallbladder cancer have ranged from 3% to 23% and mortality rates have ranged from 0% to 5% (Table 6). The current study demonstrates no perioperative mortality, 26% major morbidity rate, and a median hospital stay of only 11.5 days.

Chemotherapy and radiation therapy have not been effective in the treatment of gallbladder cancer, and adjuvant therapy after cholecystectomy or complete resection has not been encouraging.[25] In this review, 4 of 23 patients received adjuvant chemotherapy or radiation therapy. No information was gained from this small number of patients. Forty-four percent of patients in the current study recurred with peritoneal implants, emphasizing the high propensity of this tumor to seed the abdominal cavity This suggests that adjuvant intraperitoneal therapy may be worthy of investigation.

Based on our analysis and literature review, we suggest an approach to the management of gallbladder carcinoma (Fig. 5). Careful imaging before laparoscopic cholecystectomy is recommended, and any suspicious mass in the gallbladder is a contraindication to laparoscopic cholecystectomy. Initial exploration begins with evaluation for liver metastasis and peritoneal seeding. If no M1 disease is found, then N2,3 nodal basins are evaluated, and frozen sections of suspicious nodes are obtained. M1 or N2,3 disease precludes curative resection.

For a suspected T1 tumor, a simple cholecystectomy is performed and a frozen section is obtained. Confirmed T1 disease requires no further treatment. For a suspected T2 or T3 tumor, the initial resection includes an *en bloc* segment IVb + V[26] hepatic resection and complete lymph node dissection, with or without extrahepatic bile duct resection. It is essential to avoid cutting through tumor or spilling gallbladder contents at any time during the operation. Depending on the difficulty of dissection in the porta hepatis or the presence of T4 disease, hepatic lobectomy or trisegmentectomy may be required for complete resection.

The location of the tumor is an important consideration in framing the approach to resection. A tumor in the neck of the gallbladder frequently involves the common duct by direct intraductal extension or external invasion of the hepatoduodenal ligament. This often requires a common bile duct resection and may necessitate an extended liver resection to obtain clearance. Any tumor that is close to the common hepatic duct on gross examination should be resected with the common bile duct. A tumor in the fundus may be treated with a limited liver resection and no common bile duct resection. In this case, it is much easier to obtain tumor-free margins with a segmental liver resection, and the portal dissection is unencumbered by tumor or inflammation.

Complete lymph node dissection should include the posterior superior pancreatic nodes and all nodal tissue in the hepatoduodenal ligament. The common bile duct, hepatic artery, and portal vein should be skeletonized. If

Table 6. SUMMARY OF SERIES OF GALLBLADDER CANCERS REPORTED SINCE 1988*

Author	Year	N	Morbidity (%)	Mortality (%)	Survival 3 yr (%)	Survival 5 yr (%)	Survival Median (mo)	Comments
Yamaguchi[30]	1988	103	—	—	42	—	—	56 simple cholecystectomy for stage I, II
Nakamura[14]	1989	15	40	0	—	25	—	2 with Nevin's I; 13 with Nevin's V†
Donohue[22]	1990	40	13	5	—	33	43	9 stage I; 22 simple cholecystectomy
Ogura[31]	1991	984	22.7	5.3	66	51	—	127 stage I; 172 hospitals†
de Aretxabala[32]	1991	54	3	0	25	—	—	21 simple cholecystectomy; includes noncurative resections
Shirai[21]	1992	40	—	0	—	65	—	6 with stage I; 8 with noncurative resections†
Matsumoto[33]	1992	28	14.5	4	—	—	32	4 with stage I; 9 with stage IV†
Ouchi[34]	1993	25	—	0	—	61	—	7 simple cholecystectomy; 6 noncurative resections
Chijiiwa[13]	1994	32	—	—	—	53	—	5 with stage I†
Gall[17]	1994	34	—	3	—	—	31	13 simple cholecystectomy, 7 with stage I
Present series	1995	23	26	0	66	58	—	—†

* Series are heterogeneous with some including simple cholecystectomy alone, and inconsistent stage distributions.
† Includes extended cholecystectomy only (no simple cholecystectomy).

inflammation or a fatty hepatoduodenal ligament makes nodal dissection difficult, or gross nodal enlargement results in tumor close to the common hepatic duct, a common bile duct resection and reconstruction is included.

For patients who have undergone cholecystectomy with an incidental finding of gallbladder cancer on pathology, no further therapy is indicated for T1 disease. Patients with T2 or T3 disease are explored as described previously. No resection is performed for those patients found to have N2 or M1 disease. All others undergo *en bloc* liver and nodal dissection. Because of inflammation from the cholecystectomy, it is difficult to differentiate tumor from scar, and the hilar dissection and node dissection are challenging. Therefore, we often include common bile duct resection and extended hepatectomy in the patients submitted to reoperation. Patients undergoing reoperation after laparoscopic cholecystectomy should have all port sites excised.[27,28]

We are following this management scheme in a prospective fashion and hope to determine the value of this approach. A revised staging system, as described, should be more predictive of outcome than the current system, and will help in directing surgical management.

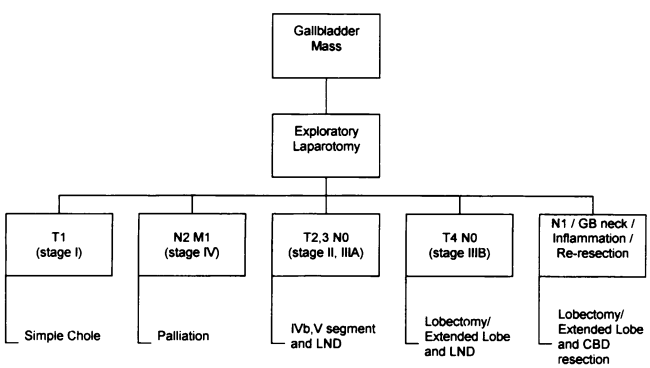

Figure 5. Algorithm for management of gallbladder cancer based on revised staging system. LND = lymph node dissection; CBD = common bile duct.

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