

Trends in Presentation and Survival for Gallbladder Cancer During a Period of More Than 4 Decades

A Single-Institution Experience

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Objectives: To determine the prevalence of incidentally found cases of gallbladder cancer, the incidence of residual disease at reexploration, and the changes in the mode of presentation, treatment, and survival of patients with gallbladder cancer during a period of more than 4 decades.

Design: Retrospective case series.

Setting: University-affiliated tertiary care center.

Patients: Between January 1, 1962, and March 1, 2008, 402 patients with gallbladder cancer were identified and their clinicopathologic data were analyzed.

Interventions: Surgical treatment, radiotherapy, and chemotherapy.

Main Outcome Measures: Incidentally discovered gallbladder cancer, incidence of residual disease, and differences in presentation, treatment, and survival.

Results: Surgical exploration was performed in 260 patients (64.7%), of whom 151 (58.1%) underwent resection. The median age of the patients was 72 years, and 72.3% were female. Between January 1, 1994, and March 1, 2008,

6881 laparoscopic cholecystectomies were performed, and there were 17 incidentally discovered cases of gallbladder cancer (0.25%). Residual disease on reexploration was identified in 0 of 2 patients with T1 tumor, 3 of 13 patients with T2 tumor, and 8 of 10 patients with T3 tumor ($P = .01$). Patients with stage IV disease (34 [13.1%] diagnosed from 1962-1979; 34 [13.1%] diagnosed from 1980-1997; and 22 [8.5%] diagnosed from 1998-2008) had a median survival of 4 months (range, 0-37 months). Concomitant liver resections increased in the third study period (11.1%, 10.1%, and 54.3%; $P < .001$), with an increase in negative margins (33.3%, 42.0%, and 63.0%; $P = .01$). Cox regression analysis identified T stage and surgical margin status as significant prognostic factors.

Conclusions: Gallbladder cancer is incidentally found during 0.25% of laparoscopic cholecystectomies. As T stage increases, the likelihood of residual disease on reexploration increases. Although many patients with gallbladder cancer present with incurable disease and have very poor survival, the overall prognosis is improving, likely because of more extensive operations.

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GALLBLADDER CANCER IS the most common malignant neoplasm of the biliary tract. The American Cancer Society estimates that about 9520 new cases of either gallbladder or bile duct cancer (excluding bile ducts within the liver) will be diagnosed in 2008 in the United States, and approximately 3340 of these people will die of their disease. Almost half of these cases are gallbladder cancer. Gallbladder cancer affects women more frequently than men and is characterized by wide geographical and ethnic variations, with a high prevalence in areas such as the Andes, Japan, and north India and among popula-

tions of Native Americans.¹⁻³ In Western countries, gallbladder cancer is closely associated with gallstone disease, whereas in Japan, it is often linked with an anomalous pancreatobiliary duct junction.²

See Invited Critique at end of article

Surgical resection is the only curative treatment. However, most patients present with advanced-stage disease and are not candidates for surgical resection. Gallbladder cancer is characterized by locally aggressive behavior, with early spread to regional lymph nodes and distant dissemination.¹⁻⁴ In addition, it recurs rapidly even

Table 1. Characteristics of 260 Patients

	Period A ^a (n=83 [31.9%])	Period B (n=105 [40.4%])	Period C (n=72 [27.7%])	P Value
Age, mean (SD), y	71 (11.4)	71 (12)	67 (13)	.03
Female sex, No. (%)	63 (75.9)	75 (71.4)	50 (69.4)	.64
Abdominal pain, No. (%)	47 (56.6)	61 (58.1)	48 (66.7)	.39
Jaundice, No. (%)	30 (36.1)	45 (42.8)	15 (20.8)	.01
Other cancer, No. (%)	11 (13.2)	21 (20.0)	14 (19.4)	.43
Tumor type, No. (%)				
Adenocarcinoma	72 (86.7)	95 (90.5)	66 (91.7)	.35
Squamous	4 (4.8)	5 (4.8)	5 (6.9)	
Other	7 (8.4)	5 (4.8)	1 (1.4)	
TNM staging, No.				
cis	1	9	1	.002
T1N0	1	3	2	.10
N1	0	0	0	
Nx	1	1	1	
T2N0	1	4	9	.16
N1	0	3	3	
Nx	6	7	5	
T3N0	3	3	5	.12
N1	4	11	7	
Nx	17	19	9	
T4N0	0	0	0	.24
N1	0	0	1	
Nx	15	11	7	
TxNxM1	34	34	22	.32

^aPeriods are defined in the "Results" section.

after presumed curative resection.^{5,6} Chemotherapy, radiotherapy, and multimodality treatment for this cancer are largely done on an empirical basis, and data from small studies regarding their efficacy are conflicting.^{1,4}

In this study, we examined the modes of presentation, surgical and adjuvant treatment, survival outcome, and changes in treatment for patients with gallbladder cancer who presented for more than 4 decades at a single institution. Our first aim was to define the prevalence of incidentally found cases of gallbladder cancer in the modern era of imaging and laparoscopic cholecystectomy. Our second aim was to define the incidence of residual disease and overall survival after resection of incidental gallbladder cancer. Our third aim was to describe the changes in management of this rare neoplasm and how these changes may affect survival.

METHODS

A retrospective review from January 1, 1962, through March 1, 2008, identified 402 patients who had been diagnosed as having gallbladder cancer. Identification of patients was done using the Research Patient Data Registry and the Tumor Registry for Massachusetts General Hospital. This study was approved by the institutional review board.

Clinical data that were evaluated included sex, age, race, smoking history, history of diabetes mellitus, history of cancer, family history of cancer, presenting symptoms, operative procedure, adjuvant therapy, sites of recurrence, and overall survival. Pathologic data that were evaluated included the TNM stage; histologic type; degree of differentiation; perineural, lymphatic, and perivascular invasion; and margin status. *Operative mortality* was defined as death within 30 days of the operation. Patients were staged according to the sixth edition of the *Cancer Staging Manual*.⁷

All available pathologic slides of the resected tumors since 1988 (88 patients) were reviewed again by 2 pathologists (V.D. and M.G.) with a special interest in the pancreatobiliary area. The Research Patient Data Registry established in 1994 was used to determine the total prevalence of laparoscopic cholecystectomies performed at Massachusetts General Hospital.

Statistical analysis of the data was done with the use of SPSS 12.0 for Windows (SPSS Inc, Chicago, Illinois). Comparisons between the 3 study periods were conducted with a 1-way analysis of variance and *t* test for continuous variables with normal distributions and the Kruskal-Wallis H test and the Mann-Whitney test for continuous variables without normal distributions as appropriate. Categorical variables were analyzed using the χ^2 test. Survival curves were constructed with the Kaplan-Meier method. Univariate comparisons were performed with the log-rank method. The Cox proportional hazards model was used for those factors found to be significant in the univariate analysis. The level of statistical significance was set at *P* = .05.

RESULTS

Between January 1, 1962, and March 1, 2008, 402 patients with gallbladder cancer were identified. We excluded 70 patients who were considered to have unresectable tumors due to metastases or locally advanced disease on imaging, 38 patients resected elsewhere who received only adjuvant treatment at Massachusetts General Hospital, and 34 patients for whom there were insufficient data. The remaining 260 patients underwent surgical exploration at our institution. These patients were diagnosed during 3 periods (1962-1979, 83 [31.9%] patients [period A]; 1980-1997, 105 [40.4%] patients [period B]; and 1998-2008, 72 [27.7%] patients [period C]), and their clinicopathologic data are given in **Table 1**.

Table 2. Residual Disease After Prior Cholecystectomy From January 1994 Through March 2008

Stage (No. of Patients)	Location of Residual Disease, No. of Patients		
	Lymph Nodes	Liver	Peritoneal Disease
T1 (2)	0	0	0
T2 (13)	2	2	0
T3 (10)	2	4	2

The median age of this cohort was 72 years (range, 11-98 years), and 72.3% were female. Most patients (233 [89.6%]) had a diagnosis of adenocarcinoma. The rest of the tumors were of squamous type (14 patients), undifferentiated carcinomas (7 patients), melanoma (1 patient), rhabdomyosarcoma (1 patient), and small cell carcinoma (1 patient), whereas 3 tumors were not further characterized (2 in period A and 1 in period B).

INCIDENTAL GALLBLADDER CANCER

From January 1, 1994, through March 1, 2008, 6881 laparoscopic cholecystectomies were performed, and in 17 patients (0.25%), gallbladder cancer was incidentally discovered. The stages of these cancers were cis (3 patients), T1 (1 patient), T2 (7 patients), and T3 (6 patients). During all 3 time periods, 32 patients underwent reexploration after a previous cholecystectomy at a median of 41 days (range, 2-84 days). Many patients underwent reexploration during period C (n=23), whereas only 7 patients did so during period A and 2 during period B ($P<.001$). The initial cholecystectomy was performed at Massachusetts General Hospital for 9 patients and at an outside hospital for 23 patients. Unresectable disease was found in 8 patients and became less frequent over time (for both periods A and B, 44.4%; for period C, 17.3%). For the 25 patients who underwent reexploration in the past 14 years, the pathologic examination slides from the initial operation were available for review. For these patients, as the T stage increased, the likelihood of residual disease at reexploration increased. Residual disease at reexploration was identified in 0 of 2 patients with T1 tumor, 3 of 13 patients (23.1%) with T2 tumor, and 8 of 10 patients (80.0%) with T3 tumor ($P=.01$). Residual disease was found for the T2 tumors in the liver in 1 patient, in the liver and a portal lymph node in 1 patient, and in the peripancreatic lymph nodes in 1 patient. For patients with T3 tumors, residual disease was found in the liver in 4 patients, in a portal lymph node in 1 patient, in the celiac nodes in 1 patient, and on the peritoneum in 2 patients (**Table 2**).

TRENDS IN PRESENTATION

In all 3 periods, 90% of patients had gallstones at presentation. The most frequent symptom on presentation in all 3 periods was abdominal pain (period A, 56.6%; B, 58.1%; and C, 66.7%; $P=.39$). Obstructive jaundice was the second most common symptom (36.1%, 42.8%, and 20.8%, respectively; $P=.01$). Jaundice at presentation signified

Table 3. Surgical Explorations for Patients With Gallbladder Adenocarcinoma

	No. (%) of Patients			P Value
	Period A ^a	Period B	Period C	
Surgical exploration	83 (100)	105 (100)	72 (100)	.03
Resection				
R0	12 (14.4)	29 (27.6)	29 (40.3)	
R1	8 (9.6)	14 (13.3)	10 (13.9)	
R2	16 (19.3)	26 (24.8)	7 (9.7)	
Unresectable				.49
Biopsy	24 (28.9)	20 (19.0)	17 (23.6)	
Palliative procedure (bypass/drainage)	23 (27.7)	16 (15.2)	9 (12.5)	

^aPeriods are defined in the "Results" section.

advanced-stage disease. Most of the 90 patients with jaundice were found to have unresectable metastatic or locally advanced tumors at exploration (period A, 20; B, 15; and C, 8) or underwent an R2 resection (9, 18, and 2, respectively). In patients who had resectable tumors (period A, 1; B, 12; and C, 5), jaundice was due to invasion of the common bile duct by the gallbladder cancer, choledocholithiasis, enlarged periportal lymph nodes, or concurrent common bile duct or pancreatic cancer. Only 38.9% (7 of 18) of the patients who underwent resection for cure had an R0 resection and only 1 patient survived longer than 2 years.

The remaining patients presented with malaise, weight loss, a palpable mass, nausea, vomiting, or a hypercoagulable state or were asymptomatic with abnormal liver function tests. TNM stratification of the patients is shown in Table 1. Carcinoma in situ was diagnosed in 11 patients. Cholelithiasis (9 patients), pancreatic cancer (1 patient), and gallbladder polyp (1 patient) were the reasons for cholecystectomy.

TRENDS IN TREATMENT

Surgical Treatment

Over time, the number of palliative resections (R2) decreased (period A, 19.3%; period B, 24.8%; and period C, 9.7%; $P=.03$) (**Table 3**). Similarly, the percentage of resections with microscopically negative margins (R0) increased (14.4%, 27.6%, and 40.3%, respectively; $P=.03$). The number of liver resections increased over time (period A, 4; B, 7; and C, 25; $P=.02$). Of the patients who underwent a liver resection, 16 underwent wedge resections of the gallbladder fossa (period A, 1; B, 6; and C, 9), 10 underwent resection of the liver segments IVb/V (all during period C), and 10 underwent a major hepatectomy (period A, 3; B, 1; and C, 6, respectively).

The overall operative mortality for curative and palliative operations decreased from 23.7% in period A to 5.5% in period C. For patients who had their tumor resected, the operative mortality decreased from 8.4% in period A to 1.4% in period C. The median length of postoperative stay during periods A, B, and C was 13, 10, and 5 days, respectively ($P<.001$).

The frequency of nodal metastasis correlated with the T stage of the cancer (0% for T1 tumors, 30% for T2 tu-

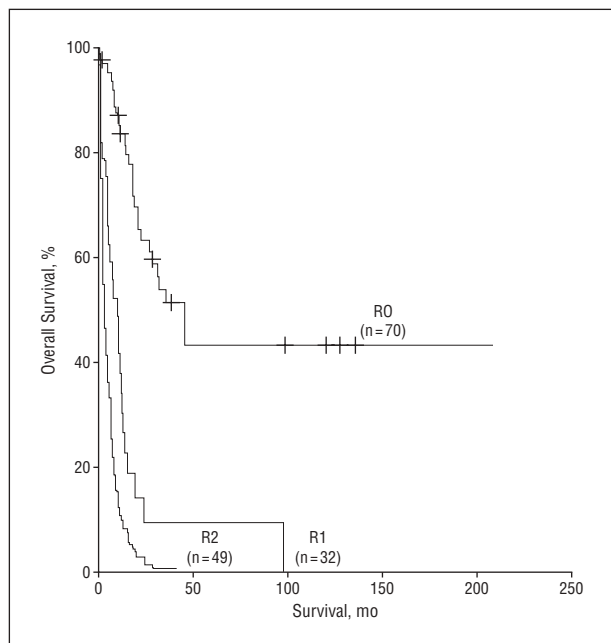


Figure 1. Negative margins have a significant effect on survival.

mors, and 66.7% for T3 tumors; $P = .002$). Patients who underwent surgical exploration and were found to have unresectable tumors had either a biopsy of the tumor, a bypass procedure (biliary bypass, gastrojejunostomy, or ileocolostomy), or a biliary drainage procedure (cholecystostomy or choledochostomy). Common bile duct resection was performed in 8 patients and did not significantly increase the number of lymph nodes resected (mean, 2.4; range, 0-10).

Chemoradiation Therapy

Overall, the use of nonsurgical therapies increased from period A to C (A, 18.1%; B, 22.8%; and C, 45.8%; $P < .001$). Chemoradiation with fluorouracil was the standard of care given to most patients during periods A and B. During period C, 45.4% of the chemotherapy regimens included gemcitabine hydrochloride. Patients received a variety of chemotherapy regimens, doses, and number of cycles, so conclusions regarding its role are difficult to make based on this retrospective data set.

Trends in Survival

Overall median survival improved from period A to C (A, 3.5 months; B, 6.5 months; C, 12 months; log-rank $P = .002$). In all 3 periods, a negative resection margin (R0) and negative lymph nodes were associated with an improved survival (R2, 3 months; R1, 10 months; and R0, 45 months; log-rank $P < .001$; N0, 45 months; N1, 18 months; log-rank $P = .008$) (**Figure 1**).

The stage of disease at presentation affected the survival in all time periods (stage I, median survival not reached; stage II, 10.3 months; stage III, 4.7 months, and stage IV, 4 months; log-rank $P < .001$) (**Figure 2**). The survival of patients who presented with advanced-stage disease and who underwent palliative procedures remained poor in all

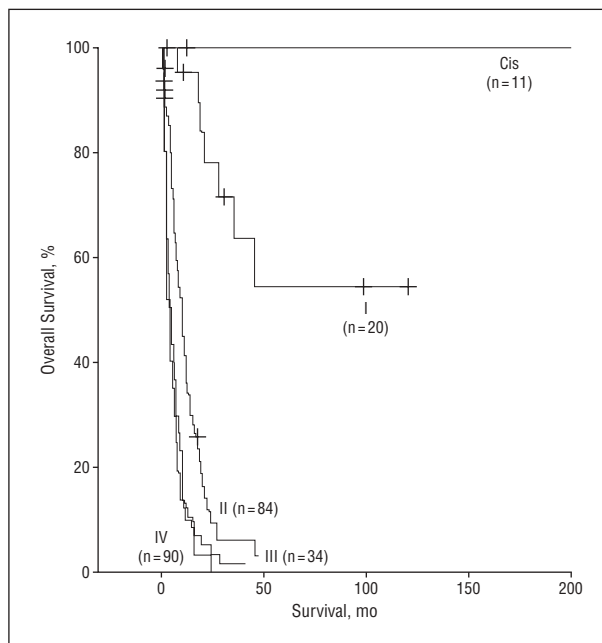


Figure 2. Overall survival by stage. Stages I, II, III, IV, and Cis are shown.

Table 4. Cox Regression Analysis of Survival Prognostic Factors

Factor	P Value	
	Univariate	Multivariate
Jaundice	.002	.12
T stage	<.001	.04
N stage	.01	.97
Resection margin (R)	<.001	.01
Vascular invasion	.02	.49
Perineural invasion	.004	.16

periods (A, 1.9 months; B, 3.9 months; and C, 3.6 months; log-rank $P < .02$). Palliative resection did not confer a statistically significant change in survival compared with no resection (median survival with no resection, 2.7 months; with R2 resection, 4 months; log-rank $P = .30$). Patients with a T2 tumor had a median survival of 35 months, and there was no significant difference in survival between those who underwent an extended re-resection and those who underwent a simple cholecystectomy. Patients with a T3 tumor had a significant improvement in survival with radical resection vs simple cholecystectomy (12 months vs 6 months, log-rank $P = .05$).

We examined the prognostic significance of the following factors: sex; prior cholecystectomy; liver resection; T stage; N stage; differentiation of the tumor; perineural, lymphatic, and venous invasion; surgical margin status; and postoperative chemoradiation therapy for patients who underwent resections with curative intent. The results of univariate and multivariate analyses for the factors that significantly influenced survival are summarized in **Table 4**. After Cox regression analysis, the margin status and the T stage of the tumor remained significant predictors of survival.

Table 5. Site of Recurrence Based on Stage of Tumor

TNM Stage (No. of Patients)	Site of Recurrence, No. of Patients			RFS, mo
	Liver/Periportal	Peritoneum	Extra-abdominal	
T2N0 (3)	0	3	0	11
T2N1 (4)	4	0	0	10
T3NX (10)	4	5	1 (Lung)	9
T3N0 (4)	2	2	0	5
T3N1 (8)	6	1	1 (Lung)	13
T3NX (10)	5	4	1 (Brain)	9

Abbreviation: RFS, recurrence-free survival.

Recurrences

Recurrent disease was documented in 39 of the 102 patients who underwent an R0 (21) or an R1 (18) resection. The time to recurrence was shorter for patients who underwent an R1 resection (8 months vs 15 months; $P=.01$). Overall, the recurrence-free survival was 22 months (range, 0.5-208 months). The sites of disease recurrence after presumed curative resection are shown in **Table 5**.

COMMENT

Gallbladder cancer is the fifth most common malignant neoplasm of the digestive tract and is associated with a very poor prognosis. This is largely attributed to the advanced stage of disease at presentation, which frequently precludes a curative resection. The overall median survival has improved for more than 4 decades, as is shown in our study. Multi-institutional and population-based studies from the United States, Japan, and Europe have reported similar conclusions regarding the advanced stage of presentation and poor outcomes of the disease.⁸⁻¹⁰

Gallbladder cancer is incidentally found during 1.5% of laparoscopic cholecystectomies and in 0.35% to 0.5% of pathology reports.¹¹⁻¹³ The number of cases of incidental gallbladder cancer found during 6881 laparoscopic cholecystectomies for the past 15 years in our series was 17 (0.25%). This lower incidence may be due to improved imaging and awareness of the disease by clinicians. When gallbladder cancer is found incidentally during or after a cholecystectomy, aggressive resection should be performed either during the present operation or during a second operation. The incidence of finding residual disease varies among studies and can be as high as 76%.¹⁴⁻¹⁷ In our series, 56% of patients who underwent reexploration were found to have residual disease. Patients underwent reexploration at a median of 41 days, similar to other series.^{14,15} Increased T stage at cholecystectomy correlated with a higher frequency of residual disease. As the initial T stage increased from T1 to T3, the risk of residual disease increased from 0% to 80%. Similar trends were seen in studies by Pawlik et al,¹⁴ Shirai et al,¹⁶ de Aretxabala et al,¹⁷ and Bartlett et al.¹⁸ None of the patients with T1 tumors were found to have residual disease, which is

consistent with studies by Shirai et al¹⁶ and Wakai et al.¹⁹ Only 23% of our patients with T2 disease had residual disease compared with reports of 56.7% by Pawlik et al,¹⁴ 40% by Shirai et al,¹⁶ 62.5% by Bartlett et al,¹⁸ and 28% by Wakai et al.¹⁹ Similar to other studies in which 77% to 100% of patients with T3 disease were found to have residual disease,^{14,16,18} 80% of our patients with T3 disease demonstrated residual disease.

Prior laparoscopic or open cholecystectomy, without spillage of bile or perforated gallbladder, does not adversely affect the survival of patients with early-stage gallbladder cancer. Fong et al¹⁵ demonstrated no difference in survival between patients with a 1-stage or a 2-stage operation. A Japanese multicenter study of 498 patients with gallbladder cancer reported that 20% experienced a perforation of the gallbladder during laparoscopic cholecystectomy, which adversely affected prognosis.²⁰ A multi-institutional international study demonstrated an overall port-site metastasis rate after laparoscopic cholecystectomy of 17.1%. These patients had early-stage T tumors and a 2-year survival of only 18.5%.¹¹ In our series, a second operation did not adversely affect overall survival; however, spillage of bile or perforated gallbladder in the first operation resulted in early peritoneal recurrence in 2 patients with T2 tumors and a poor outcome. Improved ability to diagnose gallbladder cancer preoperatively will allow more patients to be referred to major hepatobiliary centers for a definitive operation.

At our institution, ultrasonography is the most commonly used modality to image gallbladders. Features on ultrasonography that suggest the presence of a neoplastic process include a focal mass greater than 1 cm, irregular gallbladder wall thickening, direct extension of the soft tissue changes in the pericholecystic space or in the liver, biliary obstruction, regional lymphadenopathy, and other liver lesions.^{21,22} Any findings on ultrasonography suggestive of a neoplastic process should be further evaluated with magnetic resonance imaging. Patients with such imaging characteristics should be referred to a tertiary care center for a radical resection of the tumor. Patients should undergo an open cholecystectomy to minimize the chance of bile spillage with possible liver resection based on the stage of the cancer.

An aggressive surgical approach with liver resection, portal lymphadenectomy, and common bile duct resec-

tion for gallbladder cancers extending beyond the mucosa is indicated to achieve negative margins and appropriately stage the cancer. The benefit of radical resections for gallbladder cancer is well established in the literature.^{18,23-25} Extension into the adjacent liver parenchyma is frequent. In the 1960s and 1970s, surgeons were reluctant to include liver resection in the operative plan. The number of liver resections that we performed has increased, especially within the past 10 years (in 64% of resections for cure in period C compared with 17% in periods A and B each). Common bile duct resection was performed in 8 patients without increasing the median number of lymph nodes resected. A consensus has not been reached regarding the benefit of common bile duct resection as part of a radical resection.^{14,26,27} We perform a common bile duct resection only when the cystic duct margin is positive.

Overall survival has improved from 3.5 months in period A to 12 months in period C in our series. Overall median survival for patients who underwent resection (R0 and R1) was 24 months with a 5-year survival of 35%. An R0 resection significantly improved the 5-year survival to 46%. These results are similar to those seen in other Western series, such as those by Fong et al¹⁵ and Dixon et al,²⁸ in which 5-year survival rates were 38% and 35%, respectively.

Adjuvant treatment for gallbladder cancer remains largely ineffective. Published response rates are less than 30%.²⁹ Due to the rarity of this tumor, most studies are phase II clinical trials with a small number of patients. A phase III multi-institutional Japanese study evaluated the effect of postoperative adjuvant therapy with mitomycin and fluorouracil vs surgery alone in 112 patients with gallbladder cancer and demonstrated a statistically significant improvement in survival with adjuvant therapy in patients who underwent noncurative resections (5-year survival, 26% vs 14.4%; $P=.04$).³⁰ In most newer trials, gemcitabine is used either alone or in combination with other agents for advanced-stage gallbladder cancer.³¹ In our study, there is a clear trend toward the use of gemcitabine either alone or in combination with other agents. The heterogeneity of the patients and the regimens used makes it difficult to extrapolate any conclusions. A better understanding of the pathogenesis of the disease is needed to develop more effective targeted adjuvant therapy.²⁹

Incidentally discovered gallbladder cancer occurred in 0.25% of laparoscopic cholecystectomies in the past 15 years. An increased T stage increases the likelihood of finding residual disease. Patients with gallbladder cancer continue to have a poor prognosis because many of the patients present with advanced disease. Earlier detection coupled with an aggressive surgical approach leads to better outcomes. A better understanding of the molecular pathways contributing to the development of gallbladder cancer is needed to develop improved adjuvant therapies to increase overall survival.

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Author Contributions: Drs Konstantinidis, Deshpande, Genevay, Berger, Fernandez-del Castillo, Tanabe, Lauwers, and Ferrone had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Konstantinidis, Lauwers, and Ferrone. *Acquisition of data:* Konstantinidis, Deshpande, Genevay, Tanabe, and Lauwers. *Analysis and interpretation of data:* Konstantinidis, Deshpande, Berger, Fernandez-del Castillo, Tanabe, Zheng, Lauwers, and Ferrone. *Drafting of the manuscript:* Konstantinidis, Tanabe, and Ferrone. *Critical revision of the manuscript for important intellectual content:* Deshpande, Genevay, Berger, Fernandez-del Castillo, Ferrone, Tanabe, Zheng, and Lauwers. *Statistical analysis:* Konstantinidis and Zheng. *Administrative, technical, and material support:* Deshpande, Genevay, Tanabe, and Zheng. *Study supervision:* Konstantinidis and Ferrone.

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INVITED CRITIQUE

In 1978, Piehler and Crichlow reviewed the dismal outcomes of patients with gallbladder cancer, reporting a 5-year survival rate of just 4.1%, including those with incidentally discovered gallbladder cancer.¹ More than 30 years later, Konstantinidis and colleagues at Massachusetts General Hospital offer some new insights for the few patients who present with relatively early-stage disease. The results of this study add to a growing body of evidence that, for incidentally discovered gallbladder cancer, surgical reexploration with a planned major liver resection (segments V and IVA) and regional lymphadenectomy are indicated because most (50%-75%) patients with T1b, T2, and T3 gallbladder cancer will have additional disease identified at reexploration.

This study suggests that collective wisdom has been passed from one surgical generation to the next. Attempts at surgical "palliation" were less frequent in each successive time period. This likely reflects the incongruities of major surgery and successful palliation in patients with such a short survival time, less than 4 months in each period. In this series, 90 patients had jaundice before surgery and only 1 patient survived more than 2 years.

Of the cohort of 402 patients, the authors report that 260 patients (64.7%) underwent surgical exploration, and of those, 151 (37.6%) had a resection performed. Just under half (70 [46.4%]) of those patients underwent an R0 resection, with a median survival of 45 months. For patients receiving less than an R0 resection, the survival data from this series almost parallel those for patients who did not undergo surgery.

The message is clear. Aggressive surgery (liver resection and regional lymphadenectomy) plays a role in increasing the ability to achieve an R0 resection in patients with T1, T2, or T3 gallbladder cancer. For many patients who undergo surgery, R0 resection may not be

achieved and almost half of patients who had R0 resection still have recurrence. Surgeons will need to think beyond "cut more" or "go wider" and actively develop new strategies for the treatment of gallbladder cancer to affect a larger number of patients.

Surgeons in the United States need to take a closer look at the success of our colleagues overseas in improving overall cure rates for patients with a cancer that had a previously dismal prognosis, such as gastric cancer, another disease for which regional and systemic recurrences are common. By using an approach of primary systemic chemotherapy followed by surgery, Cunningham et al² reported a 5-year survival improvement of 13% for all patients who were considered surgical candidates. Perhaps primary systemic chemotherapy for patients with locally advanced gallbladder cancer or confirmed T2 or T3 gallbladder cancer before re-resection will improve survival. Alternatively, postoperative chemoradiation therapy might prove to be advantageous. Only through increased cooperation among major regional US cancer centers will new treatment strategies for infrequently encountered malignant solid tumors be provided before another 3 decades have passed.

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