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Abstract

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DISCLOSURE

None.

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Background—This study was designed to develop a more robust predictive model, beyond T-stage alone, for incidental gallbladder cancer (IGBC) for discovering locoregional residual (LRD) and distant disease (DD) at reoperation, and estimating overall survival (OS). T-stage alone is currently used to guide treatment for incidental gallbladder cancer. Residual disease at re-resection is the most important factor in predicting outcomes.

Methods—All patients with IGBC who underwent reoperation at 10 institutions from 2000 to 2015 were included. Routine pathology data from initial cholecystectomy was utilized to create the gallbladder cancer predictive risk score (GBRS).

Results—Of 449 patients with gallbladder cancer, 262 (58 %) were incidentally discovered and underwent reoperation. Advanced T-stage, grade, and presence of lymphovascular (LVI) and perineural (PNI) invasion were all associated with increased rates of DD and LRD and decreased OS. Each pathologic characteristic was assigned a value (T1a: 0, T1b: 1, T2: 2, T3/4: 3; well-diff: 1, mod-diff: 2, poor-diff: 3; LVI-neg: 1, LVI-pos: 2; PNI-neg: 1, PNI-pos: 2), which added to a total GBRS score from 3 to 10. The scores were separated into three risk-groups (low: 3–4, intermediate: 5–7, high: 8–10). Each progressive GBRS group was associated with an increased incidence LRD and DD at the time of re-resection and reduced OS.

Conclusions—By accounting for subtle pathologic variations within each T-stage, this novel predictive risk-score better stratifies patients with incidentally discovered gall-bladder cancer. Compared with T-stage alone, it more accurately identifies patients at risk for locoregional-residual and distant disease and predicts long-term survival as it redistributes T1b, T2, and T3 disease across separate risk-groups based on additional biologic features. This score may help to optimize treatment strategy for patients with incidentally discovered gallbladder cancer.

Gallbladder carcinoma is a rare disease with a poor prognosis and an estimated 5-year survival rate of 5–13 %.[1–3] Despite advances in medical therapies for gallbladder cancer, surgery remains the only potentially curative treatment option.[1,4,5] In 50–70 % of patients, gallbladder carcinoma is found incidentally following elective cholecystectomy for presumed benign disease.[6,7] Current management of IGBC is largely dictated by T-stage alone, with re-resection recommended for T1b, T2, or T3 disease.[6,8] The rationale for this is based on the observation that patients with T1b, T2, and T3 disease who undergo re-resection have better survival than those who do not.[6,7,9–11] Furthermore, up to 60 % of patients have residual disease at the time of re-resection, indicating inadequate tumor clearance by cholecystectomy alone.[6,7,12,13] Although the incidence of finding residual disease on re-resection has been shown to increase with advancing T-stage, there is some evidence that it is the presence of residual disease, and not T-stage, that ultimately dictates outcomes.[7,13] Indeed, patients with residual disease have worse survival than those who do not have residual disease, regardless of T-stage.[13] Approximately 15 % of patients have disseminated disease at the time of re-resection.[7,14]

Tumor grade, lymphovascular invasion (LVI), and perineural invasion (PNI) are important factors associated with survival in other biliary and gastrointestinal malignancies.[15–19] In IGBC, grade, LVI, and PNI have been shown in some studies to be associated with the presence of residual and/or disseminated disease at the time of re-resection, and predictive of survival.[13,14,20,21]

Due to the rarity of this disease, data often are limited by small cohorts of patients, and no studies have assessed the combined value of T-stage, grade, LVI, and PNI in predicting outcomes in patients with IGBC. The purpose of this large, multi-institutional study was to develop a predictive model using pathology data that are readily available from the initial cholecystectomy to estimate the risk of finding locoregional residual (LRD) and/or distant disease (DD) at the time of re-resection, and to predict survival in patients with IGBC.

METHODS

Study Population

The U.S. Extrahepatic Biliary Malignancy Consortium (USEBMC) represents a collaboration of ten high-volume, academic institutions: Emory University, Johns Hopkins University, New York University, The Ohio State University, Stanford University, University of Louisville, University of Wisconsin, Vanderbilt University, Wake Forest University, and Washington University in St. Louis. All patients with IGBC who underwent reoperation from January 2000 to March 2015 were evaluated. Pertinent baseline demographic, preoperative, intraoperative, pathologic, and postoperative outcome data were collected. Pathologic review was performed at each institution by experienced GI pathologists. Pathologic staging and the extent of lymph node dissection were defined as per American Joint Committee on Cancer (AJCC) 7th edition guidelines.[22] Survival information was verified with the Social Security Death Index, when appropriate. Institutional Review Board approval was obtained at each institution prior to data collection.

Only patients with IGBC and information regarding the presence of LRD and/or DD on re-exploration were included. Descriptive analyses were performed on the entire cohort. Only patients with complete data for T-stage, tumor grade, LVI, and PNI were included in descriptive and survival analyses for the proposed Gallbladder Cancer Predictive Risk Score. Thirty-day postoperative deaths were excluded for all survival analyses.

Gallbladder Cancer Predictive Risk Score

The Gallbladder Cancer Predictive Risk Score (GBRS) was developed using T-stage, tumor grade, and the presence of LVI and PNI. Each factor was assigned a value, which was added to obtain a total risk score ranging from 3 to 10. The scores were then separated into three risk groups: low (3–4), intermediate (5–7), and high (8–10) (Fig. 1).

The primary objective was to assess the predictive value of the GBRS for finding LRD and/or DD at the time of re-resection for IGBC. Locoregional residual disease was defined as the presence of tumor at the bile duct, regional lymph nodes, and the gallbladder fossa at the time of re-resection. Distant disease was defined as the presence of tumor in the liver outside the gallbladder fossa, in the peritoneum, and other distant locations. The secondary endpoint was overall survival (OS).

Statistical Analysis

All statistical analysis was conducted using SPSS 22.0 software (IBM Inc., Armonk, NY). χ^2 analysis was used to compare categorical variables, and Student's *t* test or one-way

ANOVA was used for continuous variables, where indicated. Univariable regression analyses were performed to assess the association of individual pathologic factors and GBRS with LRD and DD. Kaplan–Meier survival plots were calculated for OS. Univariable Cox regression analysis was performed to assess the effect of individual pathologic features and GBRS on OS. Statistical significance for each endpoint was predefined as $p < 0.05$.

RESULTS

Of 449 patients with gallbladder cancer, 266 (59 %) were discovered incidentally. Four patients did not have information regarding the presence of LRD or DD at reoperation and were excluded, leaving 262 patients (58 %) for analysis. Baseline demographics and clinicopathologic features are summarized in Table 1. LRD was identified in 129 patients (49 %). DD was identified in 45 patients (17 %). In 48 patients (18 %), the procedure was aborted due to the presence of distant and/or locally advanced disease. The majority of patients underwent a partial hepatectomy (segments IVb/V) with portal lymph node dissection ($n = 182$, 82 %). Most patients had T2 disease (50 %), negative margins (75 %), and were moderately differentiated (58 %). Forty-six percent of patients were positive for LVI and 53 % for PNI. Positive lymph nodes were found in 44 %. Eight patients (3 %) received neoadjuvant chemotherapy, and all had T3/T4 disease. Half of the patients ($n = 99$) received adjuvant chemotherapy.

The associations between T-stage and grade, LVI, and PNI are shown in Supplemental Table 1. All patients with Tis/T1a disease had either well- or moderately differentiated tumors and were LVI- and PNI-negative. Patients with T1b, T2, and T3/T4 disease showed greater heterogeneity and an increased association with more adverse pathologic factors, such as poor differentiation and LVI and PNI positivity.

Gallbladder Cancer Predictive Risk Score

The GBRS is detailed in Fig. 1. Eighty-eight patients had complete data regarding T-stage, grade, LVI, and PNI and were included in subsequent GBRS analysis. After adding the assigned values for each pathologic factor, 4 patients (4 %) were in the low-risk group, 42 (48 %) in the intermediate-risk group, and 42 (48 %) were in the high-risk group. Based on the additional pathologic factors, T1b patients were redistributed across low- and intermediate-risk groups, and T2 and T3/T4 patients were redistributed across intermediate- and high-risk groups (Table 2).

Locoregional Residual Disease

The prevalence of LRD at the time of reoperation increased with advancing T-stage and grade and was higher in LVI and PNI positive patients (Table 3). Each progressive GBRS group was associated with an increased prevalence of LRD at the time of reoperation (Fig. 1). On univariable logistic regression, the odds ratio (OR) for finding LRD comparing T3/T4 to T2 disease was 3.5 (95 % CI 1.9–6.3; $p < 0.001$). The OR for finding LRD comparing high to intermediate GBRS groups was 4.5 (95 % CI 1.7–11.6; $p = 0.002$; Supplemental Table 2).

Distant Disease

The prevalence of DD at the time of reoperation increased with advancing T-stage and grade and was higher in LVI and PNI positive patients compared with negative (Table 2). Each progressive GBRS group was associated with an increased prevalence DD at the time of reoperation ($p = 0.006$; Fig. 1). On univariable logistic regression, the OR for finding DD comparing T3/T4 to T2 disease was 3.0 (95 % CI, 1.3–7.0; $p = 0.01$). The OR for finding DD comparing high to intermediate GBRS groups was 12.2 (95 % CI 1.5–100.0; $p = 0.02$; Supplemental Table 2).

Survival Analysis

Median follow-up was 15.2 months (IQR 5.1–30.0). Median OS among the whole cohort was 24.8 months. Patients with DD at the time of re-resection had a median OS of 11.1 months compared with 20.7 months in those with isolated LRD, and 59.5 months in those with no additional disease ($p < 0.001$).

Advancing T-stage and grade and positive LVI and PNI were each associated with worse OS (Supplemental Fig. 1a–d). Each progressive GBRS group was associated with decreased OS (Fig. 2a). On univariable Cox regression analysis, the hazard ratio (HR) comparing T3/T4 to T2 disease was 2.2 (95 % CI 1.5–3.3; $p < 0.001$). The HR comparing high to intermediate GBRS groups was 4.6 (95 % CI 2.0–10.3; $p < 0.001$; Supplemental Table 2).

Median OS for T1b patients was not reached in either low- or intermediate-risk groups. Patients with T2 disease in the high-risk group had worse OS compared with T2 patients in the intermediate GBRS group (26.4 vs. 66.5 months; $p = 0.03$; Fig. 2b). Among T3/T4 disease, patients in the high-risk group tended to have worse OS (14.2 months) compared with T3/T4 patients in the intermediate GBRS group (23.6 months; $p = 0.22$).

DISCUSSION

Current guidelines for re-resection of IGBC are based solely on T-stage, with radical re-resection recommended for T1b, T2, and T3 disease.[8] These recommendations are largely driven by the observation that patients in these T-stage cohorts who undergo re-resection have improved survival compared with those who do not, and patients without residual disease have improved survival compared with those with residual disease.[6,7,9–13] While T-stage has been shown to be associated with both the presence of residual disease and survival in IGBC, the predictive value of T-stage alone is somewhat controversial.[6,7,13,23] Contrary to prior reports, Fuks et al. found no correlation between T-stage and residual disease, although both factors were prognostic for survival.[6] Butte et al. found that although T-stage was associated with the presence of residual disease at re-resection, only residual disease and not T-stage was predictive of survival. Furthermore, T1b and T2 patients with residual disease had significantly worse disease-free survival than T2 and T3 patients without residual disease.[13] Thus, the presence of residual disease appears to be one of the most important prognostic factors in patients with IGBC, and identifying patients at risk for residual disease is critical.

The current study represents one of the largest multi-institutional series to date of patients with IGBC who underwent reoperation. Of 262 patients, half had T2 disease, which is in line with the general T-stage distribution among IGBC patients worldwide.[12] LRD was identified in 49 % and DD in 17 % of patients at the time of reoperation, findings that mirror several previous reports.[6,7,13] As expected, patients with DD at the time of reoperation fared the worst, followed by patients with isolated LRD. Patients with neither LRD nor DD had the best outcome.

Unlike Fuks et al., we found that T-stage was associated with the presence of LRD and DD at the time of re-resection and was predictive of survival. Other factors, however, also may play a role. Tumor grade, LVI, and PNI are important pathologic factors associated with outcomes in other biliary and GI malignancies, such as hilar and intrahepatic cholangiocarcinoma, and pancreatic, gastric, appendiceal, and colorectal cancers.[15–17,19,24–27] In gall-bladder cancer, tumor grade, LVI, and PNI, in addition to T stage, have all been implicated as important prognostic factors.[13,14,20,21] Ouchi et al. observed that patients with gallbladder cancer surviving fewer than 5 years more frequently had moderate or poorly differentiated tumors and were LVI and PNI positive compared with those surviving more than 5 years.[21] Butte et al. found that IGBC patients with residual disease were more likely to have tumors with advanced T-stage and be PNI positive than those without residual disease and tended to have higher-grade tumors and be LVI-positive. However, histologic grade was the strongest predictor of survival in their study.[13] In an earlier series from Butte and colleagues, high grade also was shown to be the strongest predictor of DD at the time of re-resection, although advanced T-stage and positive LVI and PNI tended to be more frequent among patients with DD, as well.[14]

In the current series, advancing T-stage and grade and the presence of LVI and PNI were each associated with LRD and DD at reoperation. With this in mind, the proposed GBRS incorporates T-stage, histologic grade, LVI, and PNI, which are all routinely reported on pathologic analysis of initial cholecystectomy specimens and are readily available before re-resection to better risk-stratify patients with IGBC. To our knowledge, this is the largest series of patients with IGBC undergoing reoperation and the only series that examines the combined value of these pathologic factors for predicting outcomes. Each progressive GBRS group was associated with a significantly increased risk of finding LRD and DD and decreased OS. Whereas this pattern also was seen with T-stage alone, GBRS was a stronger predictor of LRD and DD on logistic regression and OS on Cox regression.

When assessing each T-stage individually, we found that by taking into account grade, LVI, and PNI, subtle pathologic variations emerged and lead to a redistribution of each T-stage across GBRS groups. Among patients with T1b disease, 78 % were in the intermediate GBRS group, a finding that falls in line with the current recommendations for re-resection in these patients. However, 22 % had well-differentiated and LVI- and PNI-negative tumors, classifying them as low-risk. For these patients with no other poor prognostic features and zero risk of finding LRD or DD, surveillance instead of re-resection may be a reasonable option.

Among patients with T2 disease, 68 % fell in the intermediate-risk and 32 % in the high-risk GBRS group. These high-risk T2 patients, who had higher grade tumors and were nearly all LVI and PNI positive, had significantly worse survival compared with the intermediate-risk T2 patients, suggesting more aggressive tumor biology that would go unaccounted for using T-stage alone. Indeed, 62 % of high-risk T2 patients had LRD and 23 % had DD at re-resection compared with only 32 and 0 %, respectively, among intermediate-risk T2 patients. Thus, it may be prudent in high-risk T2 patients to consider additional high-quality imaging, staging laparoscopy, or neoadjuvant or adjuvant therapy. Conversely, the vast majority of T3/T4 patients fell in the high-risk group. For the 19 % with more favorable pathologic features who were classified as intermediate-risk, however, an upfront surgical approach may be appropriate.

There are several limitations to this study. First, because of its retrospective nature and the small number of patients with complete pathologic data, meaningful associations and definitive conclusions are difficult to make, and further validation is needed. However, this study incorporates data from ten unique, high-volume, academic institutions across the United States, which more closely represents the disease characteristics and general practice patterns of this country and eliminates single-institution bias. Although multicenter studies often are additionally subject to poor data quality and control, a standardized database was used, data collection was monitored and interactive, and each completed institutional database was carefully vetted before inclusion for analysis. Finally, although analysis of initial cholecystectomy specimens often was performed at facilities outside the involved institutions, which may have led to inconsistencies and inaccuracies of pathologic assessment, most were re-reviewed by experienced pathologist at the participating institution. Still, details regarding certain pathologic factors, such as margin status of the original cholecystectomy specimen, were difficult to ascertain and were not included in the USEBMC dataset.

CONCLUSIONS

By accounting for subtle pathologic variations that may influence tumor biology within each T-stage, the Gall-bladder Cancer Predictive Risk Score combines T-stage with grade, LVI, and PNI to better stratify patients with incidental gallbladder cancer. Compared with T-stage alone, it more accurately identifies those at risk for locoregional residual and distant disease and better predicts long-term survival. This novel predictive risk-score may help to guide treatment strategy regarding patient selection for reoperation, staging laparoscopy, and neoadjuvant or adjuvant therapy, and external validation using a separate retrospective dataset or in the setting of a prospective clinical trial should be performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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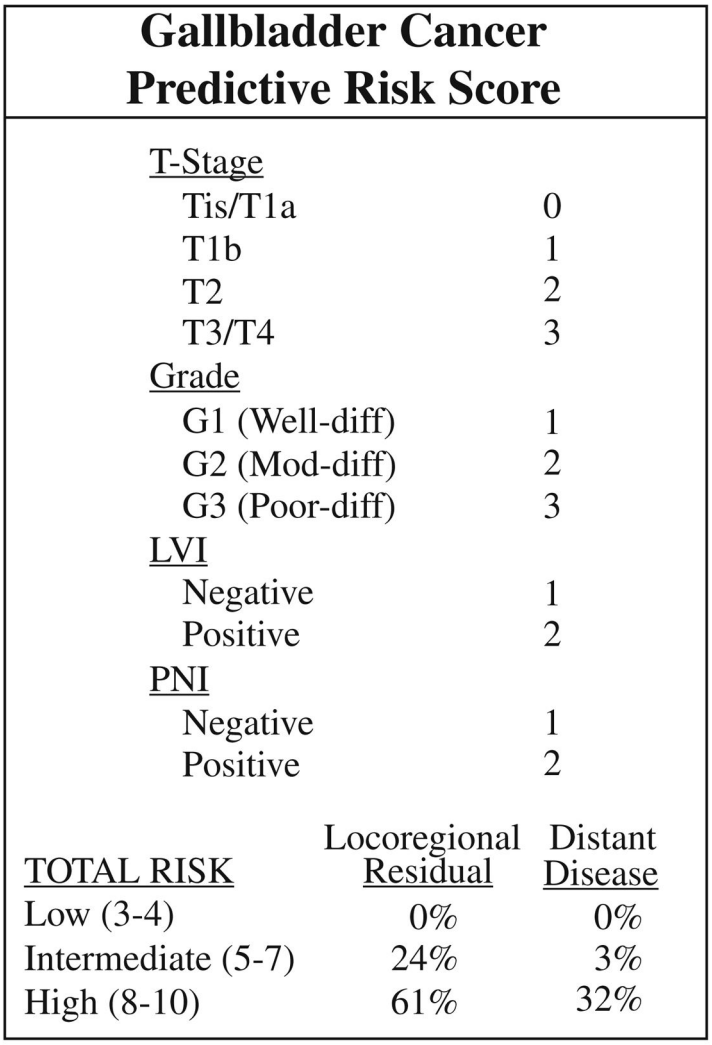

FIG. 1.

Gallbladder Cancer Predictive Risk Score (GBRS). The values for each pathologic factor are added to obtain a total risk score, ranging from 3 to 10. Patients are categorized into either the low, intermediate, or high GBRS group based on their total risk score. Each progressive GBRS group is associated with an increased prevalence of locoregional residual disease (p = 0.01) and distant disease (p = 0.006) at the time of reoperation

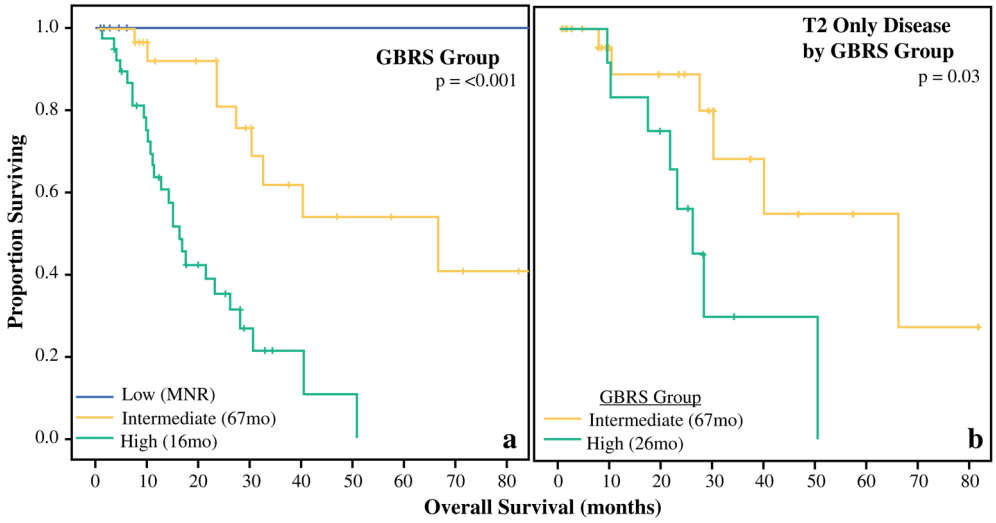

FIG. 2.

a Each progressive GBRS group was associated with a significant decrease in OS. Low-risk group ($n = 4$), intermediate-risk group ($n = 42$), and high-risk group ($n = 42$). Log-rank p value ≤0.001. **b** Overall survival was better for T2 patients in the intermediate GBRS group ($n = 28$) than T2 patients in the high-risk group ($n = 13$). Log-rank p value 0.03

TABLE 1

Baseline demographics and clinicopathologic variables of patients with incidental gallbladder cancer undergoing reoperation

Variable	All pts (n = 262)
Age (year), mean ± SD	65 ± 11.6
BMI, mean ± SD	30 ± 6.9
Race, *n* (%)	
White	190 (73)
African–American	27 (10)
Latino	15 (6)
Asian	5 (2)
Other/unknown	25 (9)
ASA class, *n* (%)	
1	2 (1)
2	63 (35)
3	107 (60)
4	6 (3)
Preoperative biliary drainage, *n* (%)	21 (8)
Location of original cholecystectomy, *n* (%)	
Participating Institution	45 (17)
Time to reoperation (weeks), mean ± SD	9.3 ± 14.3
Staging laparoscopy at reoperation, *n* (%)	52 (20)
Residual disease at reoperation, *n* (%)	129 (49)
Location of residual disease, *n* (%)	
Bile duct	21 (19)
Liver	54 (48)
Lymph node	45 (40)
Distant disease at reoperation, *n* (%)	45 (17)
Location of distant disease, *n* (%)	
Liver	8 (19)
Peritoneum	20 (47)
Both	6 (14)
Other	9 (21)
Attempted re-resection, *n* (%)	231 (88)
Completed re-resection, *n* (%)	214 (82)
Type of resection, *n* (%) (*n* = 222)	
Bile duct only	8 (4)
Cholecystectomy only	20 (9)
Partial hepatectomy[a] + Portal LND	182 (82)
Major hepatectomy	9 (4)
Common bile duct resection, *n* (%)	73 (28)
Port sites excised, *n* (%)	87 (33)

Variable	All pts (n = 262)
EBL (mL), mean ± SD	340 ± 346
Final margin status, *n* (%) (*n* = 260)	
R0	196 (75)
R1	15 (6)
R2	49 (19)
AJCC T-Stage, *n* (%) (*n* = 226)	
T1a/Tis	8 (4)
T1b	14 (6)
T2	113 (50)
T3/T4	91 (40)
Grade, *n* (%) (*n* = 195)	
Well	24 (12)
Moderate	115 (58)
Poor/undifferentiated	56 (30)
Lymphovascular invasion present, *n* (%)(*n* = 113)	52 (46)
Perineural invasion present, *n* (%) (*n* = 117)	62 (53)
Lymph nodes retrieved, *n* (%) (*n* = 236)	
Any	197 (83)
N1	197 (83)
N2	53 (23)
# Lymph nodes retrieved, mean ± SD	4.9 ± 5.5
Lymph node positive, *n* (%) (*n* = 197)	
Any	86 (44)
N1	82 (42)
N2	14 (7)
# Lymph nodes positive, mean ± SD	0.9 ± 1.4
Neoadjuvant chemotherapy, *n* (%)	8 (3)
Adjuvant chemotherapy, *n* (%) (*n* = 199)	99 (50)

BMI body mass index, *ASA* American Society of Anesthesiologists, *LND* lymph node dissection, *EBL* estimated blood loss, *AJCC* American Joint Committee on Cancer [a] Resection of liver segments IVb and V

TABLE 2

Association of T-stage with GBRS group

AJCC T-stage	GBRS group		
	Low	Intermediate	High
Tis/T1a, *n* (%)	2 (100)	0 (0)	0 (0)
T1b, *n* (%)	2 (22)	7 (78)	0 (0)
T2, *n* (%)	0 (0)	28 (68)	13 (32)
T3/T4, *n* (%)	0 (0)	7 (19)	29 (81)

AJCC American Joint Committee on Cancer, *GBRS* Gallbladder Cancer Predictive Risk Score

TABLE 3

Association of predictive factors with locoregional residual and distant disease

Predictive factors	LRD	*p* value	DD	*p* value
AJCC T-stage, *n* (%)		<**0.001**		**0.005**
T1a/Tis	0 (0)		0 (0)	
T1b	2 (17)		0 (0)	
T2	42 (40)		9 (8)	
T3/T4	60 (70)		19 (21)	
Grade, *n* (%)		**0.02**		**0.05**
Well	7 (32)		1 (4)	
Moderate	53 (51)		13 (11)	
Poor	37 (65)		13 (22)	
Lymphovascular invasion, *n* (%)		**0.004**		**0.01**
Negative	18 (33)		2 (3)	
Positive	31 (63)		10 (19)	
Perineural invasion, *n* (%)				**0.006**
Negative	19 (40)		1 (2)	
Positive	37 (63)	**0.04**	12 (19)	

LRD locoregional residual disease, *DD* distant disease, *AJCC* American Joint Committee on Cancer