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GASTROINTESTINAL

Preoperative CT findings for prediction of resectability in patients with gallbladder cancer

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Abstract

Objectives To predict residual tumor (R) classification in patients with a surgery for gallbladder (GB) cancer, using preoperative CT.

Methods One hundred seventy-three patients with GB cancer who underwent CT and subsequent surgery were included. Two radiologists assessed CT findings, including tumor morphology, location, T stage, adjacent organ invasion, hepatic artery (HA) invasion, portal vein invasion, lymph node metastasis, metastasis, resectability, gallstone, and combined cholecystitis. The R classification was categorized as no residual tumor (R0) and residual tumor (R1 or R2). We analyzed the correlation between CT findings and R classification. We also followed up the patients as long as five years and analyzed the relationship between the R classification and the overall survival (OS).

Results There were 134 patients with R0 and 39 patients with R1/R2. On multivariable analysis, liver invasion (Exp(B) = 3.19, $p = 0.010$), bile duct invasion (Exp(B) = 3.69, $p = 0.031$), and HA invasion (Exp(B) = 3.74, $p = 0.039$) were independent, significant predictors for residual tumor. When two of these three criteria were combined, the accuracy for predicting a positive resection margin was 83.38% with a specificity of 93.28%. The OS and the median patient survival time differed significantly according to the resection margin, i.e., 56.0% and 134.4 months in the R0 resection and 5.1% and 10.8 months in the R1/R2 resection group ($p < 0.001$).

Conclusions Preoperative CT findings could aid in planning surgery and determining the resectability using the high-risk findings of residual tumor, including liver invasion, bile duct invasion, and HA invasion.

Key Points

- *Liver invasion, bile duct invasion, and HA invasion were significant preoperative CT predictors for residual tumor in GB cancer.*
- *HA invasion showed the highest OR on multivariate analysis and the highest predictor point on a nomogram for predicting a positive resection margin.*
- *Association of two factors can predict positive resection margin with an accuracy of 83.38% and a specificity of 93.28%.*

Keywords Gallbladder · Neoplasm · Multidetector computed tomography · Residual tumor · Survival

Abbreviations

AJCC	American Joint Committee on Cancer
CI	Confidence interval
CT	Computed tomography
GB	Gallbladder
HA	Hepatic artery
HR	Hazard ratio
LN	Lymph node

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LR− Negative likelihood ratio
LR+ Positive likelihood ratio
NPV Negative predictive value
OS Overall survival
PPV Positive predictive value
SD Standard deviation

Introduction

Gallbladder (GB) cancer is the most common malignancy of the biliary tract and surpasses the occurrence of cholangiocarcinoma [1]. The prognosis of GB cancer remains dismal because most of the tumors are diagnosed at an advanced stage. Although the major therapeutic modality and the only curative treatment is surgical resection, only a minority of patients with GB cancer become candidates for curative resection at the time of their diagnosis [2]. However, if the tumor is completely resected, long-term survival is possible, even in locally advanced GB cancer [2]. Adjuvant chemotherapy has no survival benefit for patients with R0 resection [3]. R0 resection (curative negative resection margin) improves the survival rate for patients whatever the stage of GB cancer. Therefore, it is crucial to accurately predict the tumor R0 resectability.

With advances in surgical and medical treatment methods, the survival rate has been increasing in patients with GB cancer [4]. A recent study by Creasy et al [5] revealed that in patients with advanced GB cancer who underwent surgery, definitive resection was associated with a median overall survival (OS) of 51 months (95% CI 11.7 to 55.3) compared with 11 months (95% CI 4.1 to 23.6) for those with unresectable disease ($p = 0.003$). Several reports identified prognostic factors in patients with potentially resectable GB cancer [4, 6, 7]. For example, surgical obstructive jaundice, nodal involvement, adjacent organ infiltration, and higher tumor-node-metastasis stage had a strong correlation with poor patient survival [8]. Other recent studies have reported that the pathologic T stage, poor tumor differentiation, and surgical obstructive jaundice are accurate predictors for residual disease after surgical resection [8, 9]. In another study by Liang et al, approximately one fifth of patients with cancers present with acute cholecystitis and the prognosis in these cases was worse than otherwise [10].

Computed tomography (CT) is the most useful first-line imaging tool for detecting and staging primary GB cancer [11–13]. Whereas previously published reports regarding the resectability or prognosis of GB cancer focused mainly on pathological or clinical data, to the best of our knowledge, there have only been a few attempts to evaluate the resectability of GB cancer using only imaging [14, 15]. Therefore, the purpose of this study was to evaluate if preoperative CT features were predictive of a residual tumor after surgery for GB cancer.

Materials and methods

Patient population

Our institutional review board approved this retrospective study and waived the requirement for informed consent. We reviewed our institution's medical patient records from January 2006 through December 2012 and identified 267 patients with GB cancer who underwent surgical resection with a curative intent. We excluded 70 patients for the following reasons: CT after cholecystectomy with incidental GB cancer ($n = 24$); pre-existing malignancy other than GB cancer ($n = 18$); unavailable preoperative CT examination ($n = 6$); interval longer than one month between CT and surgery ($n = 20$); and suboptimal image quality ($n = 2$). Then, among these 197 patients with GB carcinoma, an additional 24 patients were excluded according to the final pathology as follows: carcinoma in situ lesion ($n = 8$); metastasis ($n = 2$); other rare tumors ($n = 14$) such as neuroendocrine carcinoma ($n = 6$); mixed adenocarcinoma and neuroendocrine carcinoma ($n = 2$); squamous cell carcinoma ($n = 1$); undifferentiated carcinoma ($n = 1$); and intracystic papillary neoplasm with invasive carcinoma ($n = 4$). Finally, 173 patients (76 males and 97 females; mean age, 74.61 years; age range, 50–95 years) were enrolled in our study. Surgery was performed using cholecystectomy ($n = 25$), extended cholecystectomy ($n = 131$), and palliative bypass surgery ($n = 17$).

According to the pathology report, the margin status of the surgical specimen was classified to R0 (negative resection margin, no cancer cells seen microscopically at the resection margin), R1 (microscopically positive margin), and R2 (macroscopically positive margin). Among these, R1 and R2 were defined as positive resection margin. Finally, among 173 patients with GB cancers, 134 patients were R0, 13 R1, and 26 R2. Figure 1 shows the flowchart of this study population.

Imaging techniques

One of the following, commercially available, multidetector CT scanners was used, i.e., a 16-channel scanner (Sensation 16, Siemens Healthineers [$n = 24$]) or a 64-channel and 128-channel scanner (Brilliance 64, Philips Healthcare [$n = 41$]; Definition, Siemens Healthineers [$n = 8$]; Aquilion, Canon Medical Systems [$n = 3$]). A section thickness of 3 mm with a 3-mm reconstruction interval, a field of view of 300 to 370 mm, a gantry rotation time of 0.5 s, a tube current-time product of 150 to 200 mAs, and a peak voltage of 120 kVp were used for all four CT scanners. For the 16-, 64-, and 128-detector CT examinations, there were detector collimations of 0.75, 0.625, and 0.5 mm, respectively. Table speeds of 13.5, 12.0, and 46.8 mm per rotation were used retrospectively. A total of 1.5 mL of nonionic contrast material (iopromide 370, 370 mg of iodine per milliliter) per kilogram of body weight

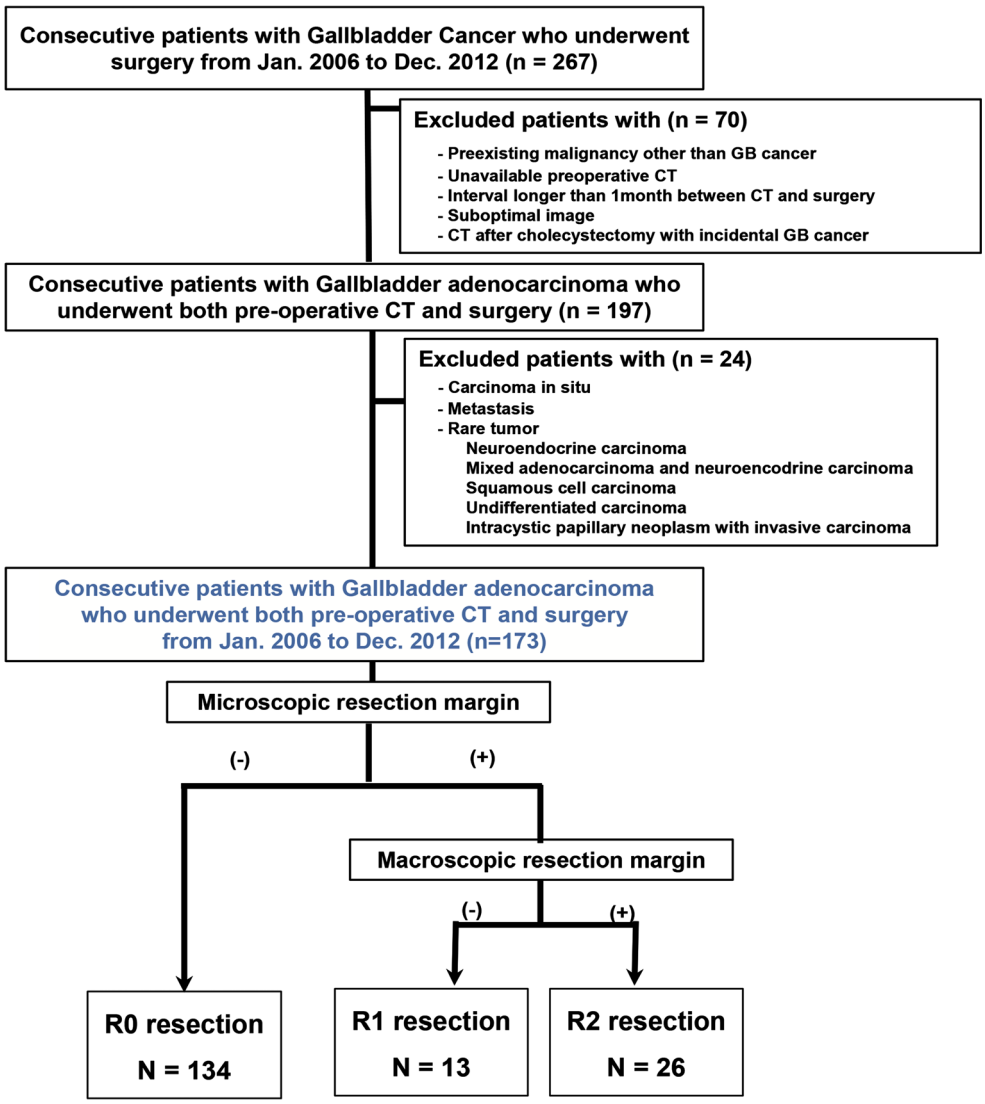


Fig. 1 Flowchart of this study population

was injected at a rate of 2.0 to 3.0 mL/s using a power injector (Multilevel CT, Medrad) with a 20-mL flush of normal saline following the contrast injection. The scanning delay for the pancreatic parenchymal phase was 22 to 24 s, after achieving enhancement of the descending aorta up to 100 HU. Hepatic venous phase scans were performed 70 s following the contrast material administration. The mean interval (± standard deviation [SD]) between the last CT examination and curative surgery was 17.35 days ± 10.02 (range 3 days to 1 month).

Imaging analysis

Two abdominal radiologists (HJ Park and SY Choi with 11 and 9 years, respectively, of clinical experience in abdominal imaging) retrospectively and independently reviewed the CT images. Both observers were aware of the diagnosis of GB cancer; however, they were blinded to the resection margin following the surgery as well as to other clinical or histopathological results for each patient.

The following imaging parameters were evaluated for qualitative analysis: (a) tumor type, i.e., mass forming, wall thickening, polypoid; (b) involved wall, i.e., hepatic side, peritoneal side, both sides; (c) invasion of adjacent organs such as the liver, bile duct, duodenum, colon, and other organs, using the loss of boundary or interface between the GB cancer and relevant organs; (d) hepatic artery (HA) invasion, evaluation considering the caliber change of a vessel in the region of tumor contact, irregularity of the vessel margin, and circumferential contiguity of the tumor or metastatic lymph node (LN) to the vessel—both abutment (less than 180° of tumor involvement of a vessel's circumference) and encasement (more than 180° of tumor involvement of a vessel's circumference) [16, 17]; (e) portal vein invasion, evaluation considering the aforementioned same two criteria and only in patients with encasement for circumferential contiguity; (f)

regional or distant LN metastasis, positive when satisfying either larger than 1 cm in the shortest diameter, internal necrosis, or spiculated margin; (g) hepatic metastasis, i.e., ill-defined, round-shaped, hypoattenuating lesion seen on unenhanced CT and peripheral enhancement on portal venous; (h) omental seeding, stranding, and thickening of omentum; (i) ascites; (j) metastasis to another organ; (k) gallstone; and (l) obstructive cholecystitis, distension of GB lumen more than 4 cm in width or 10 cm in length and thickened GB wall more than 4 mm on one side. After the first independent image analysis, interobserver agreement was assessed for each CT imaging finding. For discordant imaging findings, another radiologist (JH Kim) with 17 years of clinical experience combined the two data sets and decided which results to use after reviewing the images. Tumor size was measured by recording the longest diameter of the mass and the maximum thickness of the enhancing thickened wall in cases of wall-thickening-type cancer, and using an electronic caliper on PACS. In addition, for determination of resectability, they scored in five grades: 1, definite resectable; 2, probable resectable; 3, indeterminate; 4, probable unresectable; and 5, definite unresectable. We also followed up the patients for as long as five years and analyzed the relationship between each residual tumor classification and their OS.

Statistical analysis

Chi-square or Fisher's exact tests were used to compare the frequencies of categorical variables for the negative and positive resection margin groups. The Student *t* test was performed for continuous variables. To determine the predictors of a positive resection margin in surgical resection of GB cancer, multivariable logistic regression analysis was conducted with backward selection using the initial model which consists of the significant variables on univariable analysis. A nomogram was constructed based on this prediction model. Interobserver agreement was calculated using the weighted kappa. And weighted κ values < 0 indicated no agreement and $0 < \kappa \leq 0.2$ slight, $0.2 < \kappa \leq 0.4$ fair, $0.4 < \kappa \leq 0.6$ moderate, $0.6 < \kappa \leq 0.8$ substantial, and $0.8 < \kappa \leq 1$ almost perfect agreement. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−)

Table 1 Comparison of CT findings according to the resection margin status

Variable	R0 ($n = 134$)	R1/R2 ($n = 39$)	Total ($n = 173$)	*p*	Agreement (*k* value)
Tumor type				0.001	
Polypoid	63 (47.0%)	6 (15.4%)	69 (39.9%)		
Wall thickening	64 (47.8%)	30 (76.9%)	94 (54.3%)		
Mass forming	7 (5.2%)	3 (7.7%)	10 (5.8%)		
Tumor size (cm)	1.9 ± 1.4	1.7 ± 1.4	1.8 ± 1.4	0.245	
Involved wall				< 0.001	0.812
Hepatic side	32 (23.9%)	4 (10.3%)	36 (20.8%)		
Peritoneal side	55 (41.0%)	6 (15.4%)	61 (35.3%)		
Both sides	47 (35.1%)	29 (74.4%)	76 (43.9%)		
Liver invasion	27 (20.1%)	22 (56.4%)	49 (28.3%)	< 0.001	0.856
Bile duct invasion	11 (8.2%)	18 (46.2%)	29 (16.8%)	< 0.001	0.861
Duodenum invasion	9 (6.7%)	11 (28.2%)	20 (11.6%)	0.001	0.806
Colon invasion	12 (9.0%)	6 (15.4%)	18 (10.4%)	0.245	0.804
Other organ invasion	9 (6.7%)	5 (12.8%)	14 (8.1%)	0.313	0.785
Hepatic artery invasion	8 (6.0%)	18 (46.2%)	26 (15.0%)	< 0.001	0.817
Portal vein invasion	2 (1.5%)	6 (15.4%)	8 (4.6%)	0.002	0.851
Regional LN	55 (41.0%)	33 (84.6%)	88 (50.9%)	< 0.001	0.838
Distant LN	0 (0.0%)	8 (20.5%)	8 (4.6%)	< 0.001	0.616
Liver metastasis	1 (0.7%)	1 (2.6%)	2 (1.2%)	0.401	0.434
Omental seeding	2 (1.5%)	7 (17.9%)	9 (5.2%)	< 0.001	1.000
Ascites	4 (3.0%)	5 (12.8%)	9 (5.2%)	0.028	0.791
Other metastasis	0 (0.0%)	1 (2.6%)	1 (0.6%)	0.225	0.496
Gallstone	12 (9.0%)	5 (12.8%)	17 (9.8%)	0.541	0.690
Cholecystitis	27 (20.1%)	15 (38.5%)	42 (24.3%)	0.019	0.814

Data are presented as number (%) or mean ± standard deviation

LN lymph node

were presented with 95% confidence intervals (CIs). The 95% CIs of diagnostic performance were calculated by the exact binominal distribution for sensitivity, specificity, accuracy, PPV, NPV, and the formula provided by Simel et al [18] for positive and negative likelihood ratios. The OS rates were evaluated using the Kaplan-Meier method and compared using the log-rank test. All statistical analysis was performed using SPSS Version 25 for Windows (SPSS Inc.) and R (version 3.3.2; The R Foundation for Statistical Computing). The significance level was set at $p < 0.05$ (two-tailed).

Results

Based on the pathologic report according to the surgical specimen, among the 173 patients, 134 were assigned to the R0 group and the remaining 39 were assigned to the R1/R2 group (13 patients in the R1 group and 26 patients in the R2 group) (Fig. 1). Patient age and gender did not differ significantly according to the resection margin ($p = 0.388$ for age and $p = 0.333$ for gender).

Important CT findings for the prediction of resectability

Table 1 summarizes the frequencies of important CT findings according to the resection margin in patients with GB cancers. The tumor size was not significantly different (1.9 ± 1.4 vs. 1.7 ± 1.4 cm, respectively, $p = 0.245$) between the R0 and R1/2 groups. Table 2 summarizes the important imaging findings for the prediction of residual tumor classification. On univariate analysis, the morphologic tumor type, involved wall whether or not involving the hepatic side wall, liver invasion, bile duct invasion, duodenum invasion, HA invasion, portal vein invasion, regional LN enlargement, omental seeding, ascites, and obstructive cholecystitis were more frequently

Table 2 Important CT findings for prediction of residual tumor classification

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Tumor type		< 0.001		
Polypoid	1 (ref.)			
Wall thickening	4.92 (1.92–12.64)	0.001		
Mass forming	4.50 (0.92–22.08)	0.064		
Tumor size (cm)	0.90 (0.67–1.17)	0.456		
Involved wall		< 0.001		
Hepatic side	1 (ref.)			
Peritoneal side	0.87 (0.23–3.63)	0.842		
Both sides	4.94 (1.74–17.84)	0.006		
Involved wall[a]		0.005		
Hepatic side involvement	3.83 (1.50–9.76)			
Liver invasion	5.13 (2.42–11.14)	< 0.001	3.19 (1.31–7.72)	0.010
Bile duct invasion	9.58 (4.04–23.83)	< 0.001	3.69 (1.08–12.05)	0.031
Duodenum invasion	5.46 (2.07–14.78)	0.001		
Colon invasion	1.85 (0.61–5.15)	0.253		
Other organ invasion	2.04 (0.59–6.33)	0.226		
Hepatic artery invasion	13.50 (5.38–36.77)	< 0.001	3.74 (1.07–13.70)	0.039
Portal vein invasion	12.00 (2.63–84.50)	0.003		
Regional LN	7.90 (3.30–22.09)	< 0.001		
Distant LN	183,903,382.37 (0–NA)	0.999		
Hepatic metastasis	3.50 (0.14–89.9)	0.380		
Omental seeding	14.44 (3.31–100.07)	0.001		
Ascites	4.78 (1.20–20.24)	0.025		
Other metastasis	7,469,371.5 (0–NA)	0.986		
Gallstone	1.50 (0.45–4.34)	0.478		
Cholecystitis	2.48 (1.13–5.34)	0.021		

OR odds ratio, *CI* confidence interval, *LN* lymph node, *NA* not available

[a] Reference is defined when there is tumor involvement of only the peritoneal side

observed in the positive resection margin group ($p < 0.05$) (Fig. 2). Interobserver agreement for statistically significant imaging findings was substantial to perfect ($k = 0.434$ to 1.000). On multivariate analysis, liver invasion (odds ratio [OR], 3.19; 95% CI, 1.31–7.72; $p = 0.010$), bile duct invasion (OR, 3.69; 95% CI, 1.08–12.05; $p = 0.031$), and HA invasion (OR, 3.74; 95% CI, 1.07–13.7; $p = 0.039$) were independent, significant factors associated with the positive resection margin (Figs. 3 and 4). A regression coefficient-based nomogram was constructed from these significant variables (Fig. 5). Each factor in the nomogram was assigned a weighted number of points, and the sum of points for each patient was in accordance with a specific, predicted probability of a positive resection margin.

Table 3 summarizes the diagnostic performance of each combination of three significant findings for residual tumor classification. Among the three significant variables for predicting a positive resection margin, the specificity of HA invasion was the highest (94.03%; 95% CI, 88.58–97.39%), whereas those of liver invasion and bile duct invasion were 79.85% (95% CI, 72.05–86.28%) and 91.79% (95% CI, 85.79–95.83%), respectively. When any of the three criteria was satisfied, the sensitivity for predicting a positive resection margin was 76.92% (95% CI, 60.67–88.87%) and the specificity was 75.37% (95% CI, 67.19–82.40%). When two of the three criteria were satisfied, the sensitivity of 51.28% (95% CI, 34.78–67.58%) was identified, with the specificity of 93.28% (95% CI, 84.63–96.88%) and the highest accuracy (83.82%; 95% CI, 77.46–88.97%) of all of the combinations. When all of the three criteria were satisfied, the specificity was maximized to 97.01% (95% CI, 92.53–99.18%), although the sensitivity was lowered to 20.51% (95% CI, 9.30–36.46). When evaluating resectability by grading to 5, the AUC for evaluating the diagnostic performance of CT was 0.813 and 0.806 (95% CI, 0.726–0.901 and 0.718–0.895) in both observers, respectively. In addition, when 4 and 5 points were considered as unresectable tumors, the resectability was correctly predicted in 85.5% (148/173) and 85.0% (147/173) in both observers, respectively. Interobserver agreement for predicted resectability between the two observers was almost perfect ($k = 0.933$).

Overall patient survival according to the resection margin status

In general, the mean patient OS was 50.09 months (mean, 58.13; SD, 42.74; range, 1.80–135.90; 95% CI, 51.69–64.65). The 5-year patient survival rate of all of the included patients was 48.6% (84/173), whereas the 5-year patient survival rate in the R0 resection group was 61.2% (82/134) and that in the R1/2 resection group was 5.1% (2/39). According to the resection margin, the two groups showed a significant difference in their OS ($p < 0.001$). In the surviving patients, the mean follow-up period was 96.10 months (mean, 94.37; SD, 24.01; range, 51.7–135.9; 95% CI, 95.81–101.06). The median survival time was 134.4 months for the R0 resection group and 10.8 months for the R1/R2 resection group, respectively. The survival rate according to the resection margin status is summarized in Fig. 6.

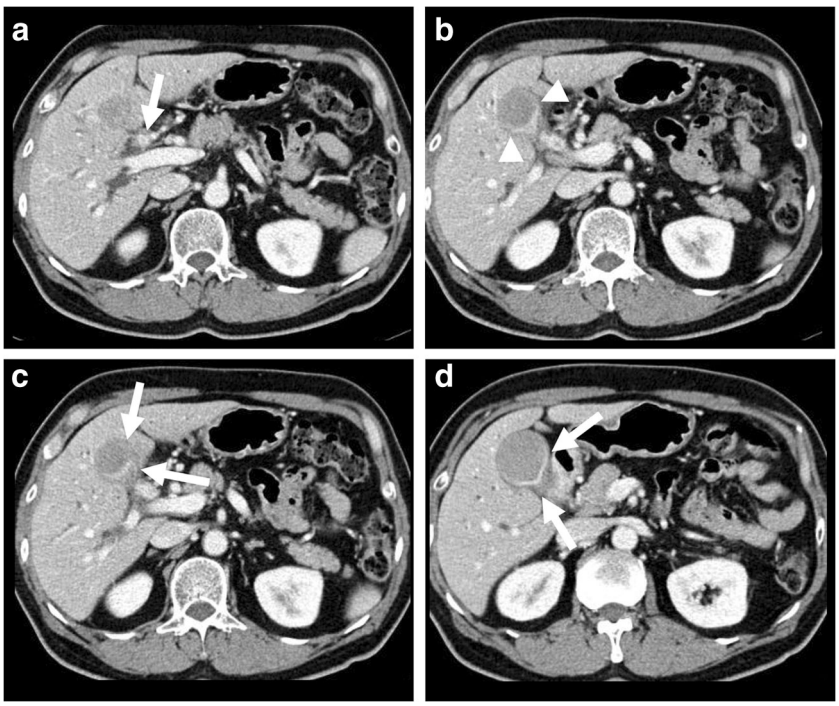


Fig. 2 GB cancer in a 69-year-old man. On preoperative CT images (**a**–**d**), GB cancer was demonstrated as enhancing wall thickening of the body and neck of the GB (arrowheads). There was loss of the fat plane with adjacent liver (arrows in **c**) and duodenum (arrows in **d**), thus suggesting direct invasion. His GB cancer extended to the common hepatic duct and abutment with the adjacent hepatic artery (arrow in **a**), thus suggesting invasion. The patient underwent extended cholecystectomy, but it turned out that it had invaded the hepatic artery and the adjacent duodenum with R2 resection being achieved

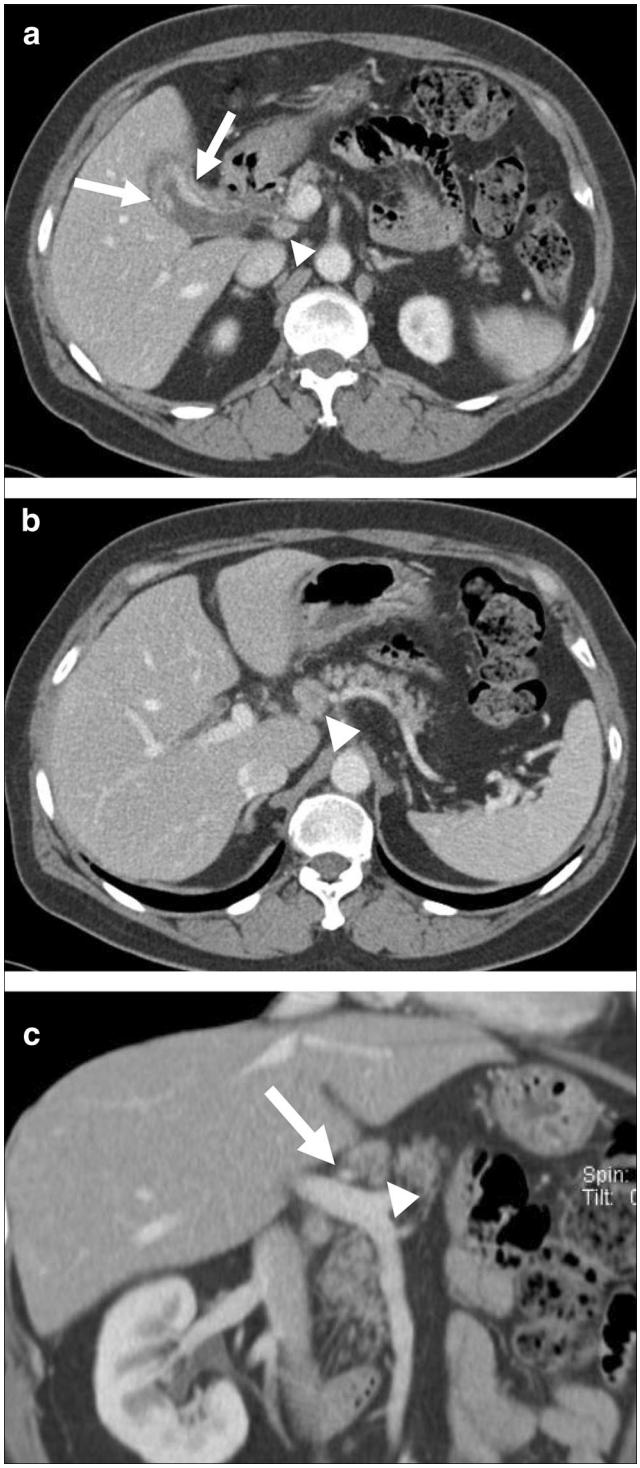


Fig. 3 GB cancer in a 69-year-old woman. On preoperative CT images (**a**–**c**), GB cancer was demonstrated as enhancing wall thickening involving both hepatic and peritoneal sides of the GB body (arrows in **a**). There was no evidence of direct liver invasion. However, enlarged lymph nodes were observed in pericholecystic (arrowhead in **a**) and common hepatic arterial (arrowheads in **b** and **c**) areas. There was abutment of the common hepatic artery by an enlarged lymph node (arrow in **c**). The patient underwent palliative cholecystectomy because paraaortic lymph node metastasis was confirmed during surgery and R2 resection was achieved

Discussion

Our study demonstrates that, among CT imaging findings, liver invasion, bile duct invasion, and HA invasion were significant independent variables for potentially predicting a positive resection margin in patients with GB cancer. Combining two or three of these criteria resulted in a specificity greater than 93.28% for predicting a positive resection margin, and which could be considered dependable for decreasing the number of unnecessary surgeries in patients with GB cancer. We also presented a nomogram for individualized risk estimation that calculates the numerical probability of a positive resection margin. After curative resection for GB cancer, patients with a negative resection margin showed higher OS rates than patients with a positive resection margin.

Extended resection with vascular resection has been performed for advanced GB cancer [19]; however, it carries a high surgical mortality rate and a poor prognosis after resection. Kobayashi et al [20] reported that invasion of HA was a poor prognostic factor in patients who had undergone radical resection for GB cancer, and they insisted that HA invasion in GB cancer should be treated the same as distant metastasis. Similarly, in our study, among three significant variables, HA invasion showed the highest OR (OR, 3.74) on multivariate analysis and the highest predictor point on a nomogram for predicting a positive resection margin. According to the well-established definition [21], on cross-sectional images, the artery is assessed as invading if abutting, whereas the vein is evaluated as invading when there is encasement or contour deformity. Accordingly, in our study, invasion of the HA was considered to be present when tumor-to-vessel contact was at least 180° or when vascular contour change was also noted. Whereas the diagnostic performance of vascular invasion has been reported as having a variable range in previous literature reports [22], the interobserver agreement for HA invasion was excellent ($k = 0.817$) in this study.

According to the American Joint Committee on Cancer (AJCC) system, T3 is defined as when the cancer has grown through the serosa and/or if it has grown from the GB directly into the liver and/or into a nearby structure outside the liver [23]. A recent study by Creasy et al [9] revealed that the T3 stage in GB cancer was an independently significant factor for predicting residual tumor after curative resection. Although the T3 stage does not only indicate liver invasion, it is presumed that this result could be strongly affected by the inevitable liver invasion. Similarly, in our study, liver invasion was one of the significant factors related to residual tumor. Another interesting point is that tumors with only the peritoneal side wall more frequently showed a negative resection margin group than others, although it was significant only in univariate analysis. Similarly, in the recently revised AJCC system (8th edition), T2 is newly subdivided into T2a and T2b depending on whether or not it is invading the hepatic

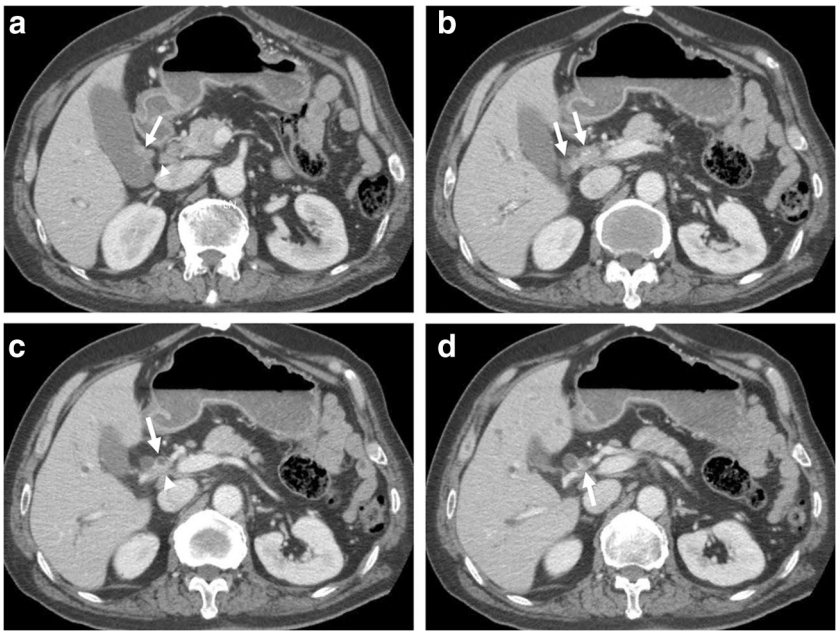


Fig. 4 GB cancer in a 76-year-old man. On preoperative CT images (**a**–**d**), GB cancer was demonstrated as focal enhancing wall thickening of the GB neck and cystic duct (arrows in **a** and **b**). The lesion was extended to the common hepatic duct (arrows in **c** and **d**) and encasement of the adjacent hepatic artery (arrowhead in **c**). An enlarged portocaval lymph node was noted (arrowhead in **a**). The patient underwent extended cholecystectomy with lymph node dissection, but it turned out that it had invaded the hepatic artery and the adjacent duodenum with R2 resection being achieved

side wall. This suggests that regardless of the presence of liver invasion, the lesion location primarily involved may significantly affect the prognosis and resectability in GB cancer.

There have been several reports studying the relationship between bile duct invasion and the prognosis in patients with GB cancer [8, 24–26]. Obstructive jaundice in GB cancer usually results from direct tumor infiltration of the extrahepatic bile duct or invasion by a metastatic LN, both of which indicating advanced disease. Accordingly, jaundice and extrahepatic bile duct involvement are independent predictors for a

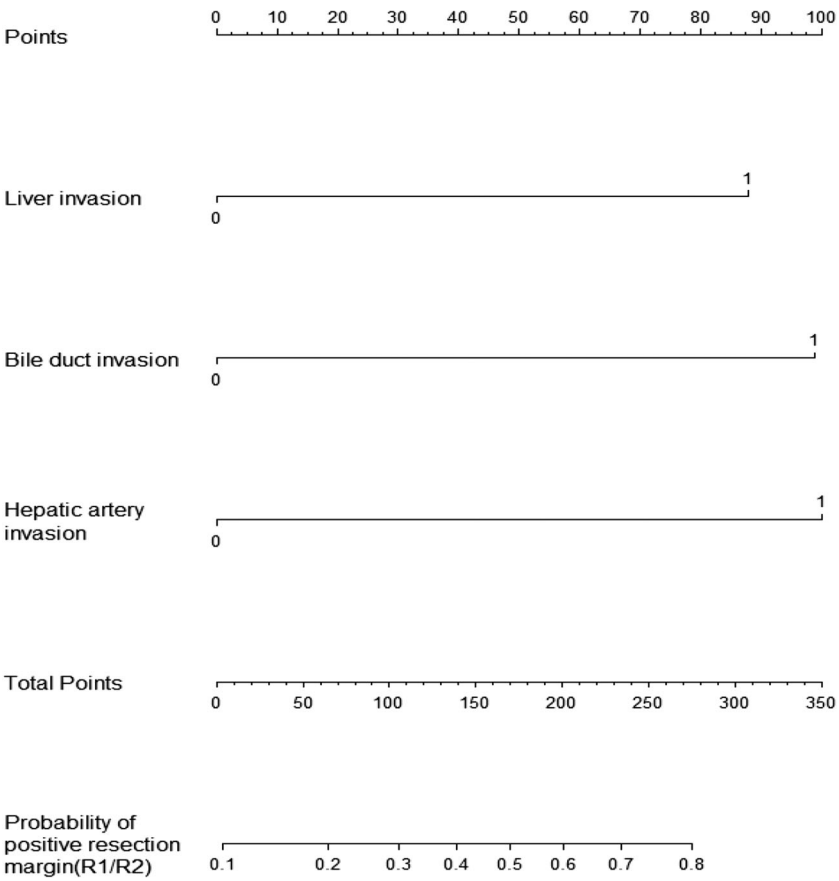


Fig. 5 Nomogram to predict the probability of a positive resection margin (R1/R2) in patients with gallbladder cancer. Predictor points are found on the uppermost point scale that correspond to each variable. On the bottom scale, points for all variables are added and translated into the probability of a positive resection margin

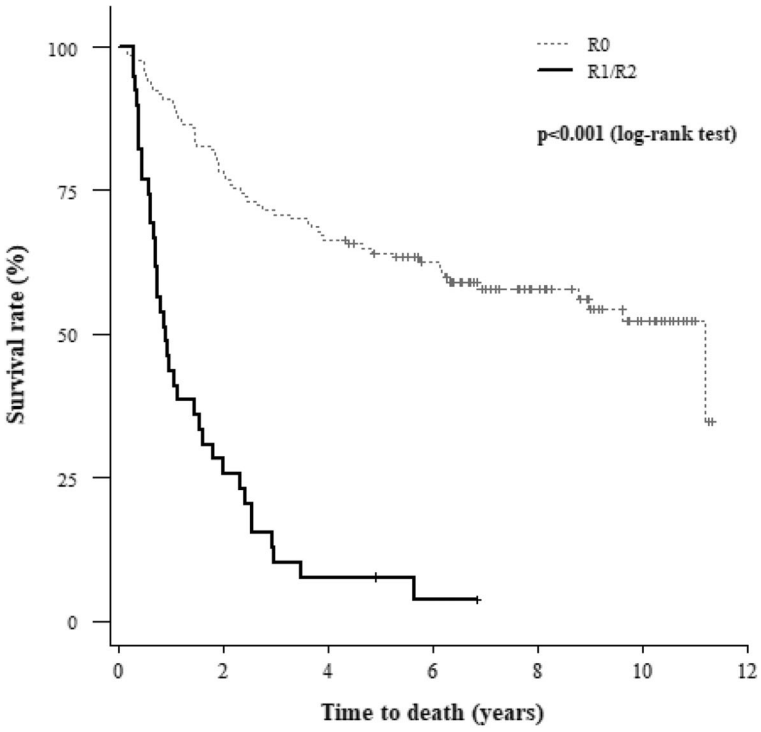
Table 3 Diagnostic performance of each combination of three significant findings for residual tumor classification

Variables	Value of diagnostic performance						
	Sensitivity	Specificity	Accuracy	PPV	NPV	LR+	LR−
Liver invasion	56.41 (22/39) (39.62–72.19)	79.85 (107/134) (72.05–86.28)	74.57 (129/173) (67.40–80.87)	44.90 (22/49) (34.52–55.74)	86.29 (107/124) (81.35–90.08)	2.80 (1.81–4.33)	0.55 (0.38–0.79)
Bile duct invasion	46.15 (18/39) (30.09–62.82)	91.79 (123/134) (85.79–95.83)	81.50 (141/173) (74.90–86.99)	62.07 (18/29) (45.82–75.99)	85.42 (123/144) (81.36–88.72)	5.62 (2.91–10.88)	0.59 (0.44–0.79)
Hepatic artery invasion	46.15 (18/39) (30.09–62.82)	94.03 (126/134) (88.58–97.39)	77.46 (134/173) (76.82–88-48)	69.23 (18/26) (51.46–82.69)	85.71 (126/147) (81.73–88.95)	7.73 (3.64–16.41)	1.57 (0.43–0.77)
Any 1	76.92 (30/39) (60.67–88.87)	75.37 (101/134) (67.19–82.40)	75.72 (131/173) (68.63–81.91)	47.62 (30/63) (39.23–56.15)	91.82 (101/110) (86.26–95.26)	3.12 (2.22–4.40)	0.31 (0.17–0.55)
Any 2	51.28 (20/39) (34.78–67.58)	93.28 (125/134) (84.63–96.88)	83.82 (145/173) (77.46–88.97)	68.97 (20/29) (52.43–81.75)	86.81 (125/144) (82.62–90.11)	7.64 (3.79–15.39)	0.52 (0.38–0.72)
All 3	20.51 (8/39) (9.30–36.46)	97.01 (130/134) (92.53–99.18)	79.77 (138/173) (73.00–85.49)	66.67 (8/12) (38.87–86.29)	80.75 (130/161) (78.10–83.14)	6.87 (2.18–21.62)	0.82 (0.70–0.96)

Data except LR+ and LR− are percentages. Data in parentheses are 95% confidence intervals

PPV positive predicted value, *NPV* negative predicted value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio

poor patient outcome and regarded as an ominous sign [26–28]. Accordingly, few studies have recommended surgical resection in such advanced disease [28, 29]. However, these studies mainly explain that the poor outcome is more related to liver function than resectability. In our study, bile duct invasion was a predictive factor for a positive resection margin in GB cancer with high specificity (91.79%) and the margin status was related to the eventual patient outcome.



Group	Median survival (month)	Survival rate(%) / No. at risk				
		Baseline	6 months	12 months	24 months	36 months
R0	134.4 (82.8-NA)	100%/134	95.5%/128	91%/122	78.4%/105	70.9%/95
R12	10.8 (8.4-19.2)	100%/39	76.9%/30	43.6%/17	28.2%/11	10.3%/4

Survival rates were calculated by Kaplan-Meier Estimates.

Fig. 6 The overall patient survival rate according to the resection margin in those patients with gallbladder cancer after curative resection. The median survival months and rates at 6, 12, 24, and 36 months in patients with a positive resection margin were significantly lower than those in patients with a negative resection margin ($p < 0.001$, compared using the log-rank test)

Therefore, this result suggests that patients with bile duct invasion should be more emphasized to undergo extensive radical resection as soon as possible.

When combining two of these three criteria features (liver invasion, bile duct invasion, and hepatic artery invasion), the sensitivity was 51.28% (20/39) and the specificity was 93.28% (125/134). However, with adding one more imaging criterion in two, whereas the specificity was slightly increased to 97.01% (130/134) and other performances including accuracy, PPV, and NPV were somewhat maintained, the sensitivity dropped to 20.51% (8/39). Therefore, we should remember that, in determining resectability of GB cancer, it is helpful to diagnose by appropriate combination of each of the three criteria, not unconditional fulfillment of all three criteria in a single case.

Various prognostic factors for GB cancer have been reported, like patient age, jaundice or bile duct invasion, liver invasion, duodenal invasion, LN metastasis, distant metastasis, vascular invasion, margin status, tumor stage, tumor differentiation, etc. [7, 8, 30, 31]. In contrast, a focus on resectability has seldom been addressed [2, 9, 15]. There is no consensus regarding the factors that make GB cancer unresectable. However, complete tumor resection (R0) remains the only successful approach for treating GB cancer and it provides the only hope for patient survival in advanced GB cancer, whenever possible. One report stated that curative surgery resulted in a survival benefit even for patients with stage IVb disease [32]. That is why R0 resection is an important prognostic factor for GB cancer [33, 34]. Therefore, according to the preoperative CT findings, R0 surgery should be planned carefully by combining surgery and neoadjuvant chemotherapy, depending on the extent of the tumor [35].

Our study has several limitations. First, there was an inevitable selection bias as the study was retrospectively designed. Second, although this study had a relatively large sample size, the number of R1/R2 (22.5% [39/173]) was small compared with R0 (77.5% [134/173]). However, as our study included only the patients who had undergone surgery with a curative intent for GB cancer, the rarity of the R1/R2 group could thus be explained. Third, we did not perform external validation by using the independent validation set. Fourth, in this study, we did not analyze the predicting factors for patient survival or early recurrence.

In conclusion, preoperative CT findings could aid in planning surgery by using the high risk findings of residual tumor, including liver invasion, bile duct invasion, and HA invasion. In addition, preoperative CT is useful for risk stratification of GB cancer, not only predicting the risk of residual tumor after surgery but also predicting poor patient survival by using important findings.

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Compliance with ethical standards

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Statistics and biometry Seo-Youn, Choi, M.D., has significant statistical expertise and no complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained (IRB No. 1702-010-829).

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

References

1. Mekeel KL, Hemming AW (2007) Surgical management of gallbladder carcinoma: a review. J Gastrointest Surg 11:1188–1193
2. Löhe F, Meimarakis G, Schauer C, Angele M, Jauch KW, Schauer RJ (2009) The time of diagnosis impacts surgical management but not the outcome of patients with gallbladder carcinoma. Eur J Med Res 14:345–351
3. Takada T, Amano H, Yasuda H et al (2002) Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 95:1685–1695
4. Miyazaki M, Itoh H, Ambiru S et al (1996) Radical surgery for advanced gallbladder carcinoma. Br J Surg 83:478–481
5. Creasy JM, Goldman DA, Dudeja V et al (2017) Systemic chemotherapy combined with resection for locally advanced gallbladder carcinoma: surgical and survival outcomes. J Am Coll Surg 224:906–916
6. Wakai T, Shirai Y, Tsuchiya Y, Nomura T, Akazawa K, Hatakeyama K (2008) Combined major hepatectomy and pancreaticoduodenectomy for locally advanced biliary carcinoma: long-term results. World J Surg 32:1067–1074
7. Agarwal AK, Mandal S, Singh S, Sakhuja P, Puri S (2007) Gallbladder cancer with duodenal infiltration: is it still resectable? J Gastrointest Surg 11:1722–1727
8. Mishra PK, Saluja SS, Prithiviraj N, Varshney V, Goel N, Patil N (2017) Predictors of curative resection and long term survival of gallbladder cancer - a retrospective analysis. Am J Surg 214:278–286
9. Creasy JM, Goldman DA, Gonen M et al (2017) Predicting residual disease in incidental gallbladder cancer: risk stratification for modified treatment strategies. J Gastrointest Surg 21:1254–1261
10. Liang JL, Chen MC, Huang HY et al (2009) Gallbladder carcinoma manifesting as acute cholecystitis: clinical and computed tomographic features. Surgery 146:861–868
11. Chen FM, Ni JM, Zhang ZY, Zhang L, Li B, Jiang CJ (2016) Presurgical evaluation of pancreatic cancer: a comprehensive

imaging comparison of CT versus MRI. AJR Am J Roentgenol 206:526–535
12. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS (2016) Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev 9:CD011515
13. Menassel B, Duclos A, Passot G et al (2016) Preoperative CT and MRI prediction of non-resectability in patients treated for pseudomyxoma peritonei from mucinous appendiceal neoplasms. Eur J Surg Oncol 42:558–566
14. Kumaran V, Gulati S, Paul B, Pande K, Sahni P, Chattopadhyay K (2002) The role of dual-phase helical CT in assessing resectability of carcinoma of the gallbladder. Eur Radiol 12:1993–1999
15. Li B, Xu XX, Du Y et al (2013) Computed tomography for assessing resectability of gallbladder carcinoma: a systematic review and meta-analysis. Clin Imaging 37:327–333
16. Al-Hawary MM, Francis IR, Chari ST et al (2014) Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 270:248–260
17. Tamm EP, Balachandran A, Bhosale PR et al (2012) Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin North Am 50:407–428
18. Simel DL, Samsa GP, Matchar DB (1991) Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol 44:763–770
19. Shimizu H, Kimura F, Yoshidome H et al (2007) Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. J Hepatobiliary Pancreat Surg 14:358–365
20. Kobayashi A, Oda T, Fukunaga K, Sasaki R, Ohkohchi N (2012) Invasion of the hepatic artery is a crucial predictor of poor outcomes in gallbladder carcinoma. World J Surg 36:645–650
21. Zaky AM, Wolfgang CL, Weiss MJ, Javed AA, Fishman EK, Zaheer A (2017) Tumor-vessel relationships in pancreatic ductal adenocarcinoma at multidetector CT: different classification systems and their influence on treatment planning. Radiographics 37: 93–112
22. Buchs NC, Chilcott M, Poletti PA, Buhler LH, Morel P (2010) Vascular invasion in pancreatic cancer: imaging modalities, preoperative diagnosis and surgical management. World J Gastroenterol 16:818–831
23. Amin MB, Edge S, Greene F et al (2017) AJCC cancer staging manual, 8th edn. Springer International Publishing, New York, NY
24. Miura F, Sano K, Amano H, Watanabe T, Takada T, Matsubara H (2012) Gallbladder cancer involving the extrahepatic bile duct. Ann Surg 255:e20
25. Nishio H, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nagino M (2011) Gallbladder cancer involving the extrahepatic bile duct is worthy of resection. Ann Surg 253:953–960
26. Hawkins WG, DeMatteo RP, Jarnagin WR, Ben-Porat L, Blumgart LH, Fong Y (2004) Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol 11: 310–315
27. Regimbeau JM, Fuks D, Bachellier P et al (2011) Prognostic value of jaundice in patients with gallbladder cancer by the AFC-GBC-2009 study group. Eur J Surg Oncol 37:505–512
28. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR (2009) Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 16:806–816
29. Higuchi R, Ota T, Araida T et al (2014) Surgical approaches to advanced gallbladder cancer: a 40-year single-institution study of prognostic factors and resectability. Ann Surg Oncol 21:4308–4316
30. Balachandran P, Agarwal S, Krishnani N et al (2006) Predictors of long-term survival in patients with gallbladder cancer. J Gastrointest Surg 10:848–854
31. Min JH, Kang TW, Cha DI et al (2019) Apparent diffusion coefficient as a potential marker for tumour differentiation, staging and long-term clinical outcomes in gallbladder cancer. Eur Radiol 29: 411–421
32. Kang MJ, Song Y, Jang JY, Han IW, Kim SW (2012) Role of radical surgery in patients with stage IV gallbladder cancer. HPB (Oxford) 14:805–811
33. Araida T, Higuchi R, Hamano M et al (2009) Hepatic resection in 485 R0 pT2 and pT3 cases of advanced carcinoma of the gallbladder: results of a Japanese Society of Biliary Surgery survey–a multicenter study. J Hepatobiliary Pancreat Surg 16:204–215
34. Pilgrim CH, Groeschl RT, Turaga KK, Gamblin TC (2013) Key factors influencing prognosis in relation to gallbladder cancer. Dig Dis Sci 58:2455–2462
35. Chaudhari VA, Ostwal V, Patkar S et al (2018) Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications. HPB (Oxford) 20:841–847